

**Executive Functioning in Multiple Sclerosis: Association
with Theory of Mind, Empathy and Quality of Life.**

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**Doctorate in Clinical Psychology
University of Edinburgh
August 2009**

Declaration

Executive Functioning in Multiple Sclerosis: association with Theory of Mind, Empathy and Quality of Life.

I declare that the present thesis is my own work and that the work of which it is a record has been done by myself. No work contained in the thesis has been submitted in application for a degree in any other institution or university. Any personal data has been processed in accordance with the provisions of the Data Protection Act 1998. All quotations have been distinguished by quotation marks and the sources of information specifically acknowledged.

Ceri Trevethan

2009

Acknowledgements

I would like to thank the following people for their help in preparation of this thesis: Dr Bruce Downey and Dr Maggie Whyte, my Clinical Supervisors and Dr Paul Morris, my Academic Supervisor for their interest, support, encouragement and guidance.

I would also like to thank Professor Louise Phillips and Professor John Crawford, University of Aberdeen for additional helpful discussions. Thanks also to Professor Crawford and Mr James Urquhart for use of the Clinimetrics Toolkit programme for statistical analyses.

Thanks to my family, friends and to Jim for your enthusiasm, care and support – very much appreciated.

Finally, thank you to all of the individuals who volunteered to take part in this study and who made this experience so interesting and enjoyable.

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Abstract

Background: Multiple Sclerosis (MS) is a chronic, degenerative, neurological condition affecting approximately 85,000 people in the UK. The impact of MS on physical abilities is well-known and there is increasing recognition of the impact of MS on mood and cognitive function. Recently MS has been linked to impaired emotion recognition and impaired Theory of Mind (ToM –the ability to attribute mental states, e.g. beliefs to oneself and others).

Methods: This study measured executive function, ToM, empathy and quality of life in an MS sample (n=42). A correlational analysis was then conducted to determine whether executive function was associated with the other variables.

Results: Two executive function measures (Mental Flexibility and Response to Feedback) were significantly associated with two ToM tasks (Revised Eyes and Stories). Mental Flexibility and the Revised Eyes ToM task were significantly associated with measures of empathy, but this effect was not present in the other executive function or ToM tasks. Neither executive functioning nor ToM measures were significantly associated with reported quality of life.

Conclusion: Overall, the MS sample demonstrated specific ToM impairment, no significant empathy impairment and widespread executive impairment relative to normative data. Low rates of depression (10%) and higher levels of anxiety (29%) were found. MS participants rated the psychological impact of MS as equivalent to the physical impact, highlighting the importance of addressing psychological aspects of MS.

Word count: 33291

Chapter 1 Introduction

1.1 Multiple Sclerosis

Multiple Sclerosis (MS) is a chronic, degenerative, neurological condition in which the immune system attacks myelin surrounding nerve fibres, damaging it and partially or completely stripping it from the fibres. This produces lesions along the nerve pathways (Compston & Coles, 2002), resulting in slowed and or ineffective transmission of electrical impulses to and from the brain. MS is primarily a disease affecting white matter - the densely packed myelinated axons which connect dispersed areas of cortical grey matter into functional, distributed neural networks. Consequently, the symptoms of MS vary and are critically dependent upon which parts of the central nervous system are affected and the specific functions of the nerves involved (Filley, 2005).

Epidemiological data indicates it is the most common cause of neurological disability in young adults, affecting approximately 85000 people in the UK (Neild, 2006). Women are almost twice as likely as men to develop MS and it is most often diagnosed between the ages of 20 and 40 (Compston & Coles, 2002). The estimated annual cost of MS in the UK is approximately £1.2 billion (Compston & Coles, 2002).

The cause(s) of MS is still unknown (Neild, 2006). Research evidence suggests that a combination of environmental and genetic factors is likely to be involved in its development. MS is not directly inherited, rather a combination of genes may make some people more susceptible to developing it (Hillert & Masterman,

2001). Reported evidence from twin studies suggests that genetic factors alone do not cause MS (Sadovnick et al., 1993).

With respect to the potential influence of environmental factors, the distinct worldwide pattern of MS cases indicates the influence of environmental factors such as bacteria or viral infection. Interestingly, the incidence and prevalence of MS increases in areas further from the equator: with a north-south gradient frequently reported (Pryse-Phillips & Costello, 2001). Among the environmental factors currently thought to increase the risk of MS, vitamin D status, infection with Epstein-Barr virus and cigarette smoking are emerging as the most consistent predictors (Ascherio & Munger, 2008).

Diagnosis of MS is typically complex due to the variety of symptoms and the importance of ruling out other conditions with similar symptomatology. Diagnosis typically involves; neurological examination and history, neuroimaging, measurement of evoked potentials and lumbar puncture (Neild, 2006). Although diagnosis previously required a minimum of two attacks, affecting more than one anatomical site, an international panel led by McDonald and colleagues (2001) published revised MS guidelines that allow diagnosis following one attack - provided there is neuroimaging evidence of lesions three months later.

1.1.1 Neuropathology of MS

MS is a chronic, inflammatory disease of the central nervous system's white matter tracts. White matter is composed of myelinated connective tissue, essential for the transfer of information between remote brain regions (Filley, 2005). The central features of MS lesions are focal demyelination, inflammation and gliosis of these communication pathways. Disability of the type described below is likely to be the result of ongoing demyelination, gliosis and axonal loss. Remission likely occurs in response to remyelination and resolution of inflammation (Lucchinetti & Parisi, 2006).

White matter has attracted renewed interest recently mainly because of evidence suggesting the involvement of white matter changes in a range of psychiatric disorders such as depression and schizophrenia, in addition to normal cognitive functioning and learning. Myelination continues into the third decade of life, is modifiable by experience, and affects information processing by regulating the velocity and synchrony of impulses between brain regions (Fields, 2008). The distributed nature of the cerebral areas involved in executive functioning and social cognition makes white matter pathology particularly relevant when it comes to the operation of these processes. This will be discussed in sections 1.6.3 and 1.7.4.

Although MS is viewed as primarily a white matter disease, there appears to be growing consensus that MS is actually associated with a combination of axonal, grey matter and white matter pathology (Lucchinetti & Parisi, 2006). Indeed, using a combination of magnetic resonance imaging and neuropsychological

assessment, (Sanfilipo et al., 2006) reported that people with MS (n=40) had smaller whole grey and white matter volume, impaired neuropsychological performance and increased neuropsychiatric symptoms compared to healthy control groups. White matter atrophy was the best predictor of processing speed and working memory whereas grey matter atrophy was associated with verbal memory performance, disinhibition and euphoria (Sanfilipo et al., 2006).

1.1.2 Types of MS

Once diagnosed, MS remains with the person for life. Some people may be only mildly affected whereas others experience a more rapid progression. Four types of MS are recognised (Neild, 2006):

1. Relapsing remitting MS

Most people are first diagnosed with this form of MS (O'Connor, 2002), which involves relapses (or attacks) followed by remission (periods of recovery). Relapses occur when inflammatory cells attack the myelin of specific nerves, (for example, inflammation in the optic nerve may result in visual problems). Relapses can last for days, weeks or months and vary in severity. Remission occurs when inflammation subsides and symptoms reduce. Although symptoms may disappear completely during remission early in MS, after several relapses there may be residual damage to the myelin, resulting in only partial recovery (Neild, 2006).

2. Secondary progressive MS

Most people initially diagnosed with relapsing remitting MS later develop secondary progressive MS (O'Connor, 2002). In secondary progressive MS there is a steady increase in disability as symptoms do not disappear completely after a relapse. Secondary progressive MS is characterised by a continued deterioration over a period of at least six months. On average, 65 per cent of people with relapsing remitting MS will develop secondary progressive MS within 15 years (Neild, 2006).

3. Benign MS

People with relapsing remitting MS who experience few relapses and fully recover between relapses can be described as having benign MS. Usually, a diagnosis of benign MS is made after 10 to 15 years of little or no disability. However, the diagnosis of benign MS remains somewhat uncertain as longitudinal evidence suggests progression in some cases over time (Sayao et al., 2007).

4. Primary Progressive MS

Primary progressive MS affects approximately 10 to 15 per cent of people with MS (Thompson et al., 2000) and is usually diagnosed in older people (Neild, 2006). It is characterised by steadily worsening symptoms and increased disability. Symptoms may continue to worsen over time or may become stable. Unlike relapsing remitting MS, this form of MS is not more likely to affect females compared to males (Thompson, 2004).

1.2 Consequences of Multiple Sclerosis

1.2.1 Sensory, Physical and Motor Difficulties

Although there is considerable variation, physical symptoms of MS can include muscle weakness, parathesias (sensations of tingling or numbness), balance problems, urinary disturbance and visual disturbances (Troster & Arnett, 2008). Some of the more common symptoms are described in Table 1 below. These physical symptoms can have a considerable impact on an individual's ability to carry out tasks of daily living or to remain in employment (Motl et al., 2008).

Table 1.1 Lesion sites and syndromes in MS

Site	Symptom	Signs
Optic nerve	Unilateral, painful loss of vision	Scotoma, reduced visual acuity, reduced colour vision
Cerebellum and cerebellar pathways	Tremor Clumsiness and poor balance	Postural and action tremor, dysarthria Limb incoordination and gait ataxia
Brainstem	Diplopia Vertigo Impaired speech and swallowing	Nystagmus Dysarthria and pseudo-bulbar palsy
Spinal cord	Weakness Stiffness and painful spasms Bladder dysfunction Erectile impotence Constipation	Increased tone and reflexes Spasticity
Other	Pain Fatigue Temperature sensitivity and exercise intolerance	

Adapted from Compston & Coles (2002:1222).

1.2.2 Cognitive Difficulties

Although the focus of clinicians and researchers has traditionally been concentrated on the physical aspects of MS, there has been increasing awareness of and interest in the impact of MS on cognition: particularly following the publication of two, large-scale, controlled studies exploring cognitive dysfunction in MS (Heaton et al., 1985; Rao et al., 1991).

Heaton and colleagues (1985) assessed neuropsychological functioning in 100 patients with either Relapsing-Remitting (RR) or Chronic-Progressive (CP) MS using the Weschler Adult Intelligence Scale (WAIS) and The Extended Halstead-Reitan Battery (HRB). Whilst both MS subgroups showed significant neuropsychological impairment compared to healthy participants (n=100), only minimal cognitive impairment was found in the RR group, whereas widespread impairment was reported in the CP group. Interestingly, the degree of neuropsychological impairment was associated with duration of MS illness. However, the differences between MS groups could not be accounted for by illness duration. Overall, 44 per cent of the clinic-based sample showed impaired neuropsychological performance compared to controls.

These findings were extended when Rao and colleagues (1991) administered a neuropsychological assessment battery to 100 patients with MS who were living in the community. Assessment of people with MS living in the community was important to explore whether clinic-based studies overestimated the frequency of cognitive impairment in the general MS population. Overall, 43 per cent of the MS sample showed impaired performance (classified as scoring at or below

the 5th percentile of the control group) compared to healthy participants (Rao et al., 1991). This is strikingly similar to the rates of impairment reported in the hospital-based sample of Heaton and colleagues (1985). The profile of impairment was not uniform within the MS group. However, at a group level MS patients were reported as being more frequently impaired on measures of recent memory, sustained attention, verbal fluency, conceptual reasoning and visuospatial perception. A degree of impairment was found on measures of language and immediate and delayed recall. In this sample, cognitive impairment was not significantly associated with either illness duration, depression, disease course or medication. There was a weak but significant correlation with physical disability (Rao et al., 1991).

Overall, the similarity in levels of cognitive impairment between the studies described above is even more notable given the differences in patient groups, assessment measures administered and the methods used to define cognitive impairment. In general, the findings suggest that impairment is typically confined to specific cognitive domains rather than presenting as a global impairment (Fischer, 2001). Bearing the above in mind, it seems reasonable to conclude that for individuals with MS there is a high probability of them experiencing cognitive impairment. However, it is important to note that cognitive changes are frequently subtle and variable and this can make them difficult to detect without specialist neuropsychological assessment.

1.2.2.1 Impact of MS on specific cognitive domains

Since the 1980s, research has indicated that cognitive impairment can be associated with MS, with prevalence rates reported between 43 and 70 percent (Peyser et al., 1980; Rao et al., 1991) at both early and late stages of the illness (Pelosi et al., 1997). As previously touched on, MS has been shown to detrimentally impact on various aspects of cognition, including attention, information processing efficiency, executive functioning, processing speed and long-term memory (Chiaravalloti & DeLuca, 2008). Whilst the heterogeneous nature of MS means that it is difficult to find consensus about which specific aspects of cognition are most affected, there appears to be some agreement that attention, processing speed and memory are most commonly affected (e.g. Calabrese, 2006; Chiaravalloti & DeLuca, 2008; Hamalainen et al., 2008; Troster & Arnett, 2008). Some authors also highlight impairment in many aspects of executive functioning (Drew et al., 2008). Including shifting, inhibition, fluency and working memory.

Although Neild (2006) noted that the majority of people with MS display subtle cognitive impairment, a recent community-based study of 95 people with MS using predicted scores and normative data reported that only 9 participants (9.47%) showed no evidence of some form of cognitive deterioration across measures of general ability (Wechsler Adult Intelligence Scales-III), executive function (Delis-Kaplin Executive Function System) and memory (Wechsler Memory Scale-III) (Drew et al., 2008). Where severe cognitive impairment has been reported it has often been characterised as a form of 'subcortical dementia' (e.g. Troster & Arnett, 2008): with features such as slow thinking

(bradyphrenia), frontal/executive dysfunction (as evidenced by difficulties with planning, set-shifting, verbal fluency and categorisation) and an impairment in verbal recall (Drew et al., 2008; Turner et al., 2002).

1.2.2.2 General ability

On measures of general ability (such as Wechsler Adult Intelligence Scales), a discrepancy between Verbal and Performance IQ, in favour of verbal IQ is most often reported (Drew et al., 2008). This discrepancy may, to some extent, reflect the task demands involved in Performance Scale subtests as many of these tests rely on motor dexterity and psychomotor speed – which can both be affected in MS. Conflicting results are reported as to whether MS participants demonstrate impaired Verbal IQ (McIntosh-Michaelis et al., 1991; Rao et al., 1991), which highlights the lack of consistency of impairment of general ability in MS, likely reflecting the heterogeneous nature of the disease (Drew et al., 2008).

1.2.2.3 Processing speed

In MS, particular difficulties with thinking quickly or following conversations are reported (Fischer, 2001). Deficits in speed of information processing are well established (e.g. Kujala et al., 1994; Litvan et al., 1988; Parmenter et al., 2007). Debate continues about the potential mediating effect of impaired processing speed on other cognitive abilities, such as working memory (DeLuca et al., 2004). Impaired transfer of information between hemispheres has also been reported (Wishart et al., 1995), with the deficit observed being likened to the generalised slowing in speed of information processing seen in normal aging.

Conceptually, this reduced 'signal to noise ratio' (Kail, 1998) would appear consistent with the impact of white matter pathology in MS (Filley, 2005).

1.2.2.4 Attention

People with MS often describe difficulties with attention. Descriptions vary from having to use more mental effort to focus on and complete tests previously performed 'automatically', to finding it more difficult to 'filter out' distractions and being unable to attend to two tests simultaneously (Fischer, 2001). Attention is a very broad term made up of a number of component processes including, attention span - focusing attention for a few seconds: divided attention - processing and responding simultaneously to more than one stimulus: selective attention - focusing on one stimulus while ignoring others: and alternating attention - quickly shifting attention from one stimulus to another (Lezak et al., 2004). Meanwhile, more complex attentional processes are more likely to be impaired in people with MS. In general, people with MS have been found to perform poorly on tests requiring them to switch attention from one stimulus to another (Heaton et al., 1985; Paul et al., 1998) and on tests requiring them to complete two tests simultaneously (D'Esposito et al., 1996).

1.2.2.5 Working Memory

Complex attention can be conceptualised as sharing aspects of working memory (Fischer, 2001). Working memory has been defined as a limited capacity system responsible for temporary storage of information (verbal – phonological loop, visual – visuospatial sketch pad) and manipulation of information (central executive) (Baddeley, 1986). As Fischer (2001) outlines, working memory is a

useful concept as it can help explain why selective attention is impaired under some conditions and not others (i.e., on tests placing more demands on working memory) and in some patient samples and not others (i.e., those whose working memory system is compromised).

Consistent with the literature on complex attention and MS, people with MS also demonstrate deficits on a range of verbal and visual tests that also involve working memory (e.g. Rao et al., 1993). There is also both performance-based and electrophysiological evidence suggesting that auditory verbal working memory may be specifically disrupted in MS (Ruchkin et al., 1994). Although it is important to acknowledge the role of individual variability in the impact of MS on attention and processing speed, it would appear that impairments in processing speed and attention can occur early in MS and may have an important impact on deficits that are identified in other cognitive domains (Calabrese, 2006).

1.2.2.6 Memory

Memory disturbance is the most frequently reported and extensively investigated cognitive impairment in MS (Fischer, 2001). Estimates suggest between 40 and 60 percent of people with MS experience memory deficits (Calabrese, 2006). Early research into memory impairment in MS characterised the memory deficits as being similar to subcortical dementia; highlighting an impairment in spontaneous verbal recall (retrieval) that can be improved with cueing (Rao et al., 1989). More recently, research highlights that the main memory problem appears to be the initial learning of new information. For

instance, DeLuca et al., (1998) reported that patients with MS required more repetitions of information to reach a predetermined learning criterion (e.g. correct recall of 10 words in two consecutive trials), and that once the information was acquired, recall and recognition were at the same level as healthy control participants.

It is important to consider that poorer learning abilities may be mediated to some degree by reduced processing speed, executive function and/or perceptual deficits (Chiaravalloti & DeLuca, 2008). Again, the heterogeneous nature of impairment associated with MS is relevant, as even meta-analyses have failed to reach consistent conclusions regarding the effect of MS on memory. A number of researchers (Thornton & Raz, 1997; Wishart & Sharpe, 1997) have reported impairments in visual and verbal learning, immediate and delayed recall and recognition. On the other hand, Zakzanis (2000) concluded that while both verbal and visual tests were impaired, recognition remained generally intact.

1.2.2.7 Executive Functioning

Executive functions comprise higher-level cognitive abilities that are required for complex goal-directed behaviour and adaptation to environmental changes or demands. These abilities include abstract reasoning, problem-solving, planning and self-monitoring (Lezak et al., 2004). A more detailed description of executive function is in Section 1.61. As a group, people with MS are reported to have an impaired ability to identify features common to a set of objects (concept formation) and to deduce rules linking items in a series (abstract reasoning) (e.g. Heaton et al., 1985). Performance may be characterised by perseverative

responding. Meanwhile, Beatty et al., (1995, 1996) reported that people with MS were able to shift conceptual frameworks when given several options, suggesting that deficits in set-shifting may be associated with a deficit in concept formation.

Previous estimates suggest that approximately 15 to 20 percent of people with MS demonstrate impaired executive functioning compared to healthy controls (Fischer, 2001; Fischer et al., 1994; Rao et al., 1991). Recently, Drew et al., (2008) investigated executive functioning in a group of 95 community-based individuals with MS in New Zealand. Drawing attention to the complexity of executive function and inconsistencies in previous investigations in MS groups, Drew et al., (2008) highlighted variability in group data and a lack of studies exploring performance on a broad range of executive functions. Indeed, factors such as these have made it difficult to gain a full understanding of the impact of MS on executive functioning and to clarify whether specific types of executive deficits are characteristic of MS. In recognition of these factors, Drew et al., (2008) examined whether there was a systematic pattern to executive function in MS by using the Delis-Kaplan Executive Function System (DKEFS; Delis et al., 2001) to provide a comprehensive assessment of executive function. As well as this, they also assessed general cognitive ability and memory.

Overall, Drew and colleagues reported that the majority of their sample (66%) of 95 people with MS showed evidence of below average performance on some aspects of executive function: a finding that is much higher than previous estimates (Fischer, 2001; Fischer et al., 1994; Rao et al., 1991). Almost two thirds

of those who demonstrated some degree of impairment only exhibited deficits on a few tests. Due to the often subtle nature of these impairments, Drew et al noted that these difficulties may not necessarily negatively impact on one's ability to complete everyday tasks. The authors further highlighted that using the DKEFS, (a more comprehensive assessment method than those used previously), may explain the increased rates of impairment compared to previous studies. Indeed, they conceded that the large number of tests administered raised the possibility that some 'impaired' scores may be due to chance. Nevertheless, 16 participants (17%) performed below average on more than five measures, indicating widespread deficits in executive function. In terms of the types of difficulties identified, these results were generally consistent with previous reports: suggesting shifting, inhibition and fluency deficits in MS (Beatty & Monson, 1996). However, as two of the measures of shifting and inhibition were timed, reduced processing speed may have impacted on performance (Drew et al., 2008). The study also highlighted that there was no 'typical' pattern of executive impairment associated with MS in the sample. This appears consistent with the majority of previous research which repeatedly emphasises the variable pattern of cognitive impairment in MS. Despite some difficulties interpreting these inconsistencies in the research findings and the need for further research in this area, it would appear evident that executive dysfunction can form an important aspect of cognitive impairment in MS. Given that executive functions are higher-level cognitive processes, the implications of impairments in EF skills are wide-ranging. Executive dysfunction can have a considerable negative impact on other aspects of cognition, and also consequences for everyday functioning. This includes

difficulties coping with novel situations, multi-tasking, inhibiting responses, switching between tasks and sequencing.

1.3 Emotion and Mood

The presence of psychological and psychiatric symptoms associated with MS was noted by Charcot, in his first descriptions of MS (Charcot, 1879, cited in Jose Sa, 2008). A significant incidence and prevalence of psychological and psychiatric symptoms in patients with MS, compared to individuals with similar degrees of disability, has been reported (Minden & Schiffer, 1990; Schiaffino et al., 1996). There has been a gradually increasing recognition of the potential impact of MS on aspects of emotional processing and mood. Consequently, an emerging body of research investigating mood disorders such as depression and anxiety, as well as issues relating to emotional regulation has begun to develop (Jose Sa, 2008).

1.3.1 Depression

The lifetime prevalence of depression in MS has been reported as approximately 50 percent (Minden & Schiffer, 1990). Depending on the study used for comparison, this rate of depression is between three and ten times that reported in the general population (Kessler et al., 1994). A meta-analysis carried out by Schubert and Foliart (1993) suggests that this is higher than in other patients with neurological conditions. Reports of symptoms of affective disorder in individuals with MS compared to those with temporal lobe epilepsy and amyotrophic lateral sclerosis revealed significantly higher levels of depression in those with MS (Schiffer & Babagian, 1984). Suicide rates amongst people with

MS are also reported to be up to seven times higher than in the general population and higher than in most neurological disorders (Sadovnik et al., 1991). These findings suggest depression in MS is not accurately characterised as purely a reaction to having a disabling, incurable and unpredictable neurological condition (Schiffer & Babagian, 1984). Although many aspects of depression in MS are the same as those found in primary depression, certain symptoms are more frequent and others less common. It is reported that irritability, discouragement and sense of frustration are more likely to accompany low mood in MS than feelings of guilt or low self-esteem (Feinstein, 2004).

Crucially, as Feinstein (2004) highlights, symptoms such as fatigue, insomnia, reduced appetite and problems with concentration and memory may be equally attributable to depression or MS - assessment of depression cannot rely solely on identification of these factors. Therefore, clarification of the potential factors associated with higher prevalence of depression in people with MS has not yet been fully explored and requires further research (Feinstein, 2004). The relationship between depression and exacerbation of MS remains unclear as there is evidence both for (Kroencke et al., 2001) and against (Dalos et al., 1983) an association. Further evidence supporting the view that depression in MS is not simply reactive comes from magnetic resonance imaging (MRI) studies, which have revealed structural (Feinstein et al., 2004) and functional (Sabatini et al., 1996) brain abnormalities associated with low mood in MS. However, psychosocial factors are also relevant, with a combination of helplessness,

uncertainty and disability important in explaining depression in MS (Lynch et al., 2001).

In studies that have explored psychological correlates of quality of life (QoL) in MS, depression has been shown to be an important predictor of QoL (Benito-Leon et al., 2002). Early studies (e.g. Rao et al., 1991) found no association between depression and cognitive dysfunction in MS. This was interpreted as suggesting that cognitive dysfunction occurred independently of depression. However these studies had numerous, methodological limitations, including small sample sizes, the use of depression rating scales that failed to reduce the confounding effects of physical MS symptoms, cognitive tests that lacked sensitivity and the inclusion of patients with mild depression. More recent research (Arnett, 2005) suggests that symptoms of depression can reduce cognitive capacity, particularly impacting on the executive function component of working memory. Concerns remain that depression in MS is frequently under-recognised and under-treated (Bieske et al., 2008). This is perhaps surprising given the evidence suggesting pharmacological treatment (Mohr et al., 2001) and psychological interventions such as cognitive-behavioural therapy can be beneficial (see Thomas et al., 2007), to the extent that it can result in significant improvement in QoL (Hart et al., 2005).

1.3.2 Anxiety

Less research into the relationship between anxiety and MS symptoms has been conducted. The reported prevalence of anxiety in MS has varied from 19 up to 90 percent (Jose Sa, 2008). High rates of anxiety in newly diagnosed MS patients

(34%) and their partners (40%) have been reported (Janssens et al., 2003). Evidence suggesting ongoing anxiety comes from a two-year longitudinal study, which found that high rates of anxiety continued after diagnosis (Janssens et al., 2006). A study of 140 consecutive MS patients reported a lifetime prevalence for any anxiety disorder of 35.6 percent: with generalised anxiety disorder (18.6%), panic disorder (10%) and obsessive compulsive disorder (8.6%) being the most frequent diagnoses. Risk factors include being female, having a diagnosis of depression and experiencing limited social support (Korostil & Feinstein, 2007). Despite high rates of occurrence, anxiety disorders are frequently overlooked in MS and consequently under treated (Korostil & Feinstein, 2007).

Zorzon et al., (2001) investigated the relationship between specific brain areas (using structural MRI) and the occurrence of anxiety in patients with MS (n=95) by comparing them to patients with chronic rheumatoid diseases (n=97) and healthy controls (n=110). They concluded that the lack of any significant association between anxiety symptoms and MRI abnormalities suggested that anxiety in MS is a reactive, psychological response. Perhaps consistent with this interpretation, McCabe (2005) suggested a link between Relapsing-Remitting MS and patients' experience of anxiety. Jose Sa (2008) also argues that high rates of anxiety in MS seem understandable given the chronic and unpredictable course of MS, and the continuous adjustment of the patient's sense of self.

1.3.4 Other mood disorders in MS

Bipolar affective disorder has been reported as being more prevalent in MS compared to the general population in both retrospective (Schiffer et al., 1986) and prospective studies (Edwards & Constantinescu 2004). However, the relationship between MS and Bipolar Affective Disorder appears complex and there is currently little specific research in this area (Jose Sa, 2008).

Although euphoria is not common in MS, it has been reported in severely disabled MS patients and seems to be associated with cognitive impairment and the presence of extensive brain lesions (Ron & Logsdail, 1989). Pseudobulbar palsy (pathological laughing and crying) has been reported in ten percent of MS patients (Feinstein et al., 1999). It has been linked to prefrontal cortex dysfunction and is mainly found in those with severe disability, cognitive impairment and longer disease duration (Feinstein et al., 1999).

1.4 Quality of Life in MS

The World Health Organisation (WHO) defines quality of life (QoL) as “an individual’s perception of their position in life in the context of the culture and value systems in which they live, and in relation to their goals, expectations, standards and concerns” (WHO QoL Group, 1994). Measurement of QoL therefore involves gaining an understanding of how satisfied a person is with their life and situation, making QoL an inherently subjective and personal issue (Skevington et al., 2004). Health-related quality of life (HQoL) has been defined as “the capacity to derive satisfaction from meaningful behaviour despite disease” (Meyers et al., 2000). Research has shown that people with MS

consistently report significantly lower QoL and HQoL scores compared to healthy controls (Nortveldt et al., 1999; Wynia et al., 2008) and compared to people with other chronic illnesses (Hermann et al., 1996). Various studies have examined factors associated with HQoL in MS and have reported that poor HQoL was predicted by progressive disease course, physical disability, self-reported fatigue, depression and cognitive impairment (Benedict et al., 2005).

Quality of life is a multi-dimensional concept, comprising a number of dimensions. These dimensions include (1) physical functioning (2) psychological function (3) social relations and (4) environment (Skevington et al., 2004). Some research has now begun to draw preliminary conclusions in terms of the impact of clinical variables (e.g. physical health and mood) on specific aspects of QoL in MS, although accurate measurement of QoL across a range of domains is complex. HQoL was strongly predicted by physical disability when the physical aspects of HQoL were emphasised (Nortvedt et al., 1999). Other researchers have shown that depression may account for more variance in QoL than other factors such as disability scores (Expanded Disability Status Scale – EDSS) or disease duration (Fruehwald et al., 2001).

Benedict et al., (2005) overcame some of these methodological difficulties when they investigated HQoL in 120 MS patients and included multiple measures in their analysis. Using linear and logistic regression, they reported that physical HQoL was predicted by fatigue, depression and physical disability. Meanwhile, Mental HQoL was associated with depression and fatigue, whereas vocational status was predicted by performance on three cognitive tests, conscientiousness

and disease duration (Benedict et al., 2005). Overall, the authors concluded that self-report measures of QoL in MS were most predicted by depression. Vocational status was predicted mainly by measures of cognitive function (Benedict et al., 2005).

More recently, the impact of cognitive and emotional factors on QoL in MS has been demonstrated by evidence that cognitive failures and emotion regulation styles are important predictors of QoL (Phillips et al., 2008). Specifically, a higher frequency of attentional lapses predicted lower QoL across all domains - even after disease severity was controlled for. Phillips and colleagues also found that greater use of emotion reappraisal strategies was related to better psychological and environmental QoL. These findings suggest that there are two separate influences on QoL in MS: physical-motor problems and cognitive-emotional problems (Phillips et al., 2008).

Further evidence of the importance of psychological aspects of QoL in MS comes from a large-scale study (n = 530) using multiple regression, which reported that “impairments in mental functions” was the most important predictor of QoL in their MS sample (Wynia et al., 2008). The results highlighted above demonstrate the often negative impact of MS on many aspects of QoL. Recent research emphasises the importance of widening the focus from mainly the physical domain, to include those relating to cognitive and emotional aspects, in order to begin to fully understand the holistic impact of MS on QoL.

1.5 Treatment for MS

Treatment for MS typically involves a number of different specialists from a multidisciplinary team (NICE, 2003). Specialists may provide treatment for specific symptoms such as mobility, co-ordination, continence or memory problems (Neild, 2006). Treatment may also include disease modifying drugs to reduce the frequency and severity of relapses, and steroids to quicken recovery following relapse (Tremlett et al., 1998). Although still controversial, many patients with MS use complementary and alternative medicines in addition to or instead of conventional medicine (Apel-Neu & Zettl, 2008).

Although diagnosis of MS may be met with relief because symptoms are finally understood, the shock of diagnosis, particularly at a young age can be considerable (Neild, 2006). The ongoing challenge of adjusting and adapting to the uncertainty that comes with MS remains an important issue for the individual and their family (Jose Sa, 2008).

1.6 Executive Functions

The reported effect of MS on executive functions has already been summarised in section 1.2.2.7. Given the focus of this study, more detailed discussion of executive functions follows.

1.6.1 What are Executive Functions?

Although the term ‘executive functioning’ is widely used in neuropsychology, the concept itself is still evolving and remains open to debate. In particular, consensus on what executive functioning actually involves and specification of

the neuronal mechanisms associated with this 'system' continues to be an ongoing and active research area (Salthouse, 2005). The following examples of definitions of executive functioning illustrate some of the uncertainty about this hypothesised system as well as highlighting some unifying themes.

"Executive functions are those involved in complex cognitions, such as solving novel problems, modifying behaviour in the light of new information, generating strategies or sequencing complex actions" (Elliot, 2003, p.50).

"The executive functions consist of those capacities that enable a person to engage successfully in independent, purposive, self-serving behaviour" (Lezak et al., 2004, p.42).

"The term executive functions...[is]...used to refer to higher-order cognitive capacities, for example, judgement, decision-making, planning, and social conduct" (Tranel et al., 1994, p.126).

Essentially, executive functions can be conceptualised as the complex processes by which an individual optimises performance in situations requiring coordination of a range of cognitive processes (Baddeley, 1986). Executive functions have been described as the brain's 'conductor', directing regions to perform or be silent, thereby orchestrating overall activity (Goldberg, 2001). Conceptualising executive functions in this 'supervisory' role is consistent with theories of executive function that portray these functions as involving a

“Central Executive” (Baddeley & Hitch, 1974; Baddeley, 2000) or a “Supervisory Attentional System (Norman & Shallice, 1986; Shallice & Burgess, 1996). These theoretical accounts emphasise that executive functions are not linked to specific cognitive domains but have a metacognitive, supervisory or controlling role. Executive functions are particularly associated with goal-directed behaviour: such as setting goals, formulating and implementing plans to achieve goals, as well as reviewing performance and adapting in response to feedback (Lezak et al., 2004). They also have a role in selective attention, sustained attention, dividing attention to carry out more than one test concurrently, shifting attention and self-monitoring (Lezak et al., 2004).

1.6.2 The neuroanatomy of executive functions

The importance of the frontal lobes in relation to ‘higher’ cognitive functions was famously highlighted by the case of Phineas Gage (Harlow, 1868). Amazingly, Gage survived a severe and significant brain injury to his left frontal lobe when a 3 foot long tamping iron blasted through his skull. Gage demonstrated dramatic personality and behaviour change and altered planning and organisational abilities (McMillan, 1986). Observations of the impact of brain injury on executive functions have continued to play a vital part in increasing our understanding of the roles of these functions, and the neuroanatomical structures and neurological processes serving them (Elliot, 2003).

There is considerable converging evidence from the neuropsychological literature that successful performance on tests of executive functions is critically

dependent on the frontal cortex (Elliot, 2003). Indeed, the terms 'frontal lobe function' and 'executive function' have often been used synonymously (Elliot, 2003). However, the term Dysexecutive Syndrome (DES) was introduced (Baddeley & Wilson, 1988) as an alternative to the anatomically based 'frontal-lobe syndrome'. Separation of anatomy/localisation and function is important, as focusing on a specific brain region is somewhat misleading and more restrictive than focusing on function (Baddeley 2002). Importantly, use of the term DES rather than frontal lobe function reflects the contemporary view that regions and connections outwith the frontal lobes also contribute to executive functions: important given the rich connections between the frontal lobes and other subcortical and cortical structures. Advances in neuroimaging, which enables investigation of executive functions in healthy individuals as well as in patients, highlights the importance of distributed circuitry rather than discrete structures (Elliot, 2003).

The intimate relationship between executive functions and the frontal lobes has been slow to emerge. This may reflect the fact that no clinical condition frequently results in specific and focal damage to the frontal lobes (Stuss & Alexander, 2000). For instance, frontal lesions following traumatic brain injury often involves several sites of damage and may include secondary diffuse injury (Stuss & Alexander, 2000). Another complicating factor relates to the fact that tests of executive function are often multi-factorial (i.e. tap several different aspects of performance). Therefore, patients with frontal lobe injury may show impaired performance for reasons other than frontal lobe dysfunction (Wilson et al., 1998) or varying deficits associated with frontal lobe injury.

Neuropsychological test performance is also likely to be affected by the symptoms of DES, such as impaired concentration and attention (Wilson et al., 1998).

Despite the theoretical, clinical and experimental difficulties associated with research into the relationship between the concept of executive function and frontal cortex, there is increasing evidence that different cognitive processes can indeed be related to distinct regions of the frontal lobes (Stuss et al., 2002). Penfield (1954) described three anatomical divisions of the frontal lobes: the motor strip (fine co-ordination of movement), pre-motor area (overall organisation of movement) and the prefrontal region. Altogether, research has gradually demonstrated that executive functions are associated with the prefrontal region of the frontal lobes, although whether all aspects of executive function are localised to this region remains unclear (Ward, 2006).

Although many clinical cases are mixed in terms of localisation of cortical damage and clinical presentation, there is evidence for three 'prefrontal syndromes' that might reflect the three anatomically distinct regions (orbital/interior, medial/cingulate and lateral) of the prefrontal cortex (Fuster, 2001; Stuss et al., 2002). As in the case of Phineas Gage (Damasio et al., 1994), lesions of the orbital prefrontal cortex appear associated with impulsive, disinhibited behaviour as well as severe attentional disorder, resulting in inability to resist distraction (Fuster, 2001). Lesions of the medial region of the prefrontal cortex (which includes the anterior cingulate) may result in difficulty initiating movement and speech as well as apathy, and problems with

concentration (Fuster, 2001). Lesions of the lateral region appear to be associated with the many cognitive deficits usually associated with frontal lobe damage, such as deficits in planning and strategy formation, problem-solving, multi-testing and disorganised behaviours (Stuss et al., 2002).

1.6.3 White matter damage or disruption and executive functioning

Although the focus is often on the impact of cortical, grey matter damage on executive function, the potential impact of damage/disruption to white matter on executive function is also vital (Fields, 2008), particularly given the dense connectivity of white matter in the frontal lobes. The importance of white matter for frontal lobe functioning and its potential impact on executive functioning is shown by studies of development and ageing (Filley, 2005). The developmental process of increased myelination is known to be important for development of executive decision-making (Liston et al., 2006). In contrast, the ageing process may involve a progressive reduction of white matter volume. This is proposed to account for changes associated with normal ageing such as slowed speed of information processing, diminished attentional capacity and forgetfulness (Filley & Cullum, 1994). White matter pathology and executive functions both also appear to be related to aspects of emotional and possibly social processing. Indeed, Filley (2005) notes that over 100 different disorders associated with white matter pathology (including those with a genetic, demyelinating, infectious, inflammatory, toxic, vascular, traumatic and metabolic aetiology) are associated with some form of cognitive or emotional dysfunction.

1.7 Social Cognition

Social interaction is an essential part of human experience. The success of human interaction depends upon the ability to detect cognitive and emotional process in others (Vollm et al., (2006). Social cognition broadly refers to the processes by which people understand themselves and others (Beer & Ochsner, 2006). A full concept of social cognition includes information processing about people (including the self) and about the norms and procedures of the social world. The processes involved in social cognition are likely to occur at both automatic and controlled levels of processing and will also be influenced by motivational biases. Processes involved in social cognition can be grouped into three parts (Beer & Ochsner, 2006):

- (i) processes involved in perceiving other people
- (ii) processes involved in perceiving oneself, and
- (iii) social knowledge.

The processes involved in perceiving other people include multiple stages of processing, such as receiving information from sensory channels to process verbal and non-verbal cues, labelling of cues to provide psychological meaning (e.g. smile or frown) and integration of information from cues with additional contextual information or stored information from previous social encounters (Beer & Ochsner, 2006). Motivational biases also impact on social cognition. For example, if we expect a person to be angry we may perceive a frown when it does not exist. Some researchers (Adolphs, 2001; Kihlstrom & Klien, 1994) highlight the importance of considering processes involved in perceiving the

self in social cognition because, like other people, the self is a social object that needs to be understood. Also, people appear to use similar processes to understand themselves as those involved in understanding other people (Bern, 1972).

Evidence from developmental psychology suggests commonalities between development of processes involved in perception of self and others. For instance, both self- and other- perception are first evident as physical activity (e.g. shared attention – Baron-Cohen, 1995) and become more complex as cognition develops (e.g. the ability to represent the mental states of others and infer differences between the self and other – Wimmer & Perner, 1983). The self has also been conceptualised as functioning as a ‘filter’ through which others are perceived. For example, reflection on personal experiences can be used to make inferences about the intentions and emotions of others, either consciously or unconsciously (Nickerson, 1999). The self can also be used as a reference point from which to organise representations about others (Beer & Ochsner, 2006). These examples demonstrate how knowledge and representations of the self (self-beliefs) can serve as an ‘anchor point’ from which to understand others (Epley et al., 2004).

Another important component of social cognition is the stock of social knowledge that enables people to successfully negotiate life events and tests (Wood et al., 2003). This knowledge consists of both declarative and procedural knowledge that can be expressed and accessed explicitly and implicitly. Declarative knowledge is characterised by a person’s ability to state what they

know about the social world, for example, facts about social norms, relations and phenomena. Procedural knowledge is characterised by skills and strategies that enable people to select an appropriate response or action according to their social environment. For example, blowing one's nose is more politely done on a tissue rather than a shirt sleeve (Beer & Ochsner, 2006). These forms of knowledge are used together to interact successfully in the social world. Clearly, social cognition is complex and involves a number of different aspects. Three important components of social cognition are emotion recognition, "Theory of Mind" and empathy – each of which will be briefly reviewed below.

1.7.1 Emotion Recognition

It could be argued that emotions have been overlooked in neuropsychology, perhaps because the cognitive psychology tradition focuses on computer-based models of information-processing. However, modern cognitive neuroscience conceptualises emotions as a product of brain activity. Consequently, they have been seen as appropriate for empirical research. Recognising the emotional states of others is an important component of social interaction: as our own emotional response or the emotional response of others may be used to regulate behaviour (Ward, 2006).

One of the most influential ethnographic studies of emotions which compared the way emotional expressions were categorised and posed across different cultures concluded that there are six basic emotional categories, existing independently of culture (Ekman & Friesen, 1976). These are happiness, sadness, disgust, anger, surprise and fear. Alternative approaches (e.g. Rolls,

2000) have suggested a dimensional rather than a categorical classification. However, evidence for fine-grained dissociations in emotion recognition, (for example, selective impairment of fear recognition following amygdala damage (Adolphs et al., 1994) and impairment in anger recognition after damage to the ventral striatum (Calder et al., 2004)) supports the categorical approach.

Autistic spectrum disorders (ASD) such as Asperger's Syndrome (AS) and High-Functioning Autism (HFA) are characterised by impairment in social interaction, including a difficulty with forming relationships and a lack of understanding of emotions and mental states (Kuusikko et al., 2009). Impaired recognition of emotions from facial expressions compared to age-matched healthy controls has been demonstrated in children and adults with ASD, particularly for negative emotions such as fear (Ashwin et al., 2007; Kuusikko et al., 2009). However, findings are not conclusive as some studies have reported that children with autism have been equally as able as typically developing children to recognise emotions (e.g. Back et al., 2007). Unfortunately, the use of different stimuli across different studies makes the results difficult to interpret. Impaired facial emotion recognition compared to healthy controls has also been reported in Schizophrenia, although the specificity, extent and nature of the deficits remain unclear (e.g. Edwards et al., 2002). There is also evidence for decline in emotion recognition with ageing (e.g. Ruffman et al., 2008).

Recognition of more complex emotions such as jealousy, pride, embarrassment and guilt have been viewed as somewhat different to basic emotions that are easily recognisable from viewing a person's face. Recognition of more complex

emotions may also imply awareness of another person's attitude to oneself or awareness of oneself in relation to other people (Blakemore et al., 2004), suggesting that more complex emotions may require more sophisticated attributional abilities.

1.7.2 Theory of Mind

A central process thought to be involved in social cognition is 'Theory of Mind'. The term 'Theory of Mind' (ToM) was originally introduced by primatologists Premack and Woodruff (1978) to account for their findings that chimpanzees could solve tests which involved inferring the mental states of other chimpanzees. ToM was defined as the ability to attribute mental states to themselves and others. Premack and Woodruff (1978) proposed that this ability is appropriately named a 'theory' because mental states are not directly observable and because the system can be used to make predictions about the behaviour of other organisms. The term was then adopted by child psychologists to refer to the development of mental perspective-taking in infants and young children (e.g. Leslie, 1987).

The concept of ToM also became influential in relation to psychopathology, when impaired ToM was suggested as an explanation for behavioural symptoms in children with ASD (Baron-Cohen et al., 1985). It is now widely acknowledged and supported by many empirical studies that autistic children and adults with Asperger's Syndrome have profound and specific difficulties with understanding the mental states of others (e.g. Baron-Cohen, 1991; Baron-Cohen et al., 1997; Buitelaar et al., 1999). Although the situation is less clear

regarding other psychiatric and psychopathological conditions, there is growing evidence for impaired ToM abilities in schizophrenia (originally proposed by Frith, 1992 and confirmed by others including Janssen et al., 2003; Mazza et al., 2001), as well as other disorders relating to frontal lobe functioning including frontotemporal dementia (e.g. Lough et al., 2006) and psychopathy (Blair & Cipolotti, 2000).

Although there is well-replicated evidence for a decline in executive functioning with increasing age (e.g. MacPherson et al., 2002; Wecker et al., 2000), age effects on ToM have been unreliable (Bull et al., 2008). Some studies report improvements in ToM with age (Happe et al., 1998), while some report stability (MacPherson et al., 2002) and yet others a decline (Maylor et al., 2002). Although Maylor et al. (2002) reported a decline in executive functioning and ToM with age, they did not report an association between the two impairments.

Separation of executive function and ToM is complex and finding an association or not between the two concepts is likely to rely partly on the measures selected (German & Hehman, 2006). Using a dual-task paradigm, Bull et al., (2008) directly addressed the issue of processing commonalities between executive function and ToM. They found that secondary tests, particularly those involving inhibition, resulted in detriments in ToM performance. These results were interpreted as suggesting that executive processes were involved in relatively simple ToM tests (e.g. understanding emotions from visual stimuli – Revised Eyes Test Baron-Cohen et al., 2001) as well as ToM tests involving complex social understanding such as consideration of multiple perspectives, inhibition

of self-knowledge and consideration of beliefs in relation to subsequent actions or emotions (e.g. Stories Test, Slessor et al., 2007). These findings are strengthened by recent, consistent evidence from McKinnon and Moscovitch (2007), also using a dual-test paradigm. Furthermore, reports of processing overlaps between executive functions and ToM in neuropsychological studies (e.g. Stone et al., 1998), developmental studies (e.g. Carlson et al., 2002) and ageing studies (e.g. German & Hehman, 2006) also lend further support to the hypothesis that executive processes are involved in ToM abilities.

Although the concept of ToM is widely used and frequently explored in research, some methodological concerns have been raised. For instance, criticisms of aspects of specific tests thought to measure ToM have been made. Bearing this in mind, a particular criticism argues that completion of ToM tests requires abilities other than ToM, such as executive functioning abilities (e.g. Bloom & German, 2000; de Gelder, 1987). Although the relationship between ToM and executive function remains unclear, the idea that all aspects of ToM can be explained by executive functioning does not seem to adequately account for all of the evidence relating to ToM abilities. For example, evidence that people with high-functioning autism often perform within normal limits on assessments of executive functioning (e.g. Baron-Cohen et al., 1999) and that brain lesions can selectively disrupt ToM abilities without impacting on executive function (e.g. Fine et al., 2001). These findings are consistent with a conceptualisation of executive functions as being perhaps necessary for ToM, although not sufficient. This view is consistent with the shift from early conceptions of ToM that emphasised the modular, domain-specific social

processing involved, excluding a role for executive functions (Baron-Cohen, 1995; Fodor, 1992) to more recent ideas that social understanding is likely to involve both modular and domain-general processes, such as executive functions (e.g. Leslie et al., 2004; 2005).

1.7.3 Empathy

Empathy refers to the ability to appreciate and share the emotional experiences of others (Gallese 2001). Empathy is viewed as being multi-dimensional: involving affective, cognitive and motivational processes (Davis, 1980; Preston & DeWaal, 2002). Although the terms 'Theory of Mind' and empathy are at times used synonymously, the aspect of *sharing* the emotional experiences of others is what distinguishes empathy (Gallese et al., 2004).

Some authors distinguish between 'cognitive empathy' and 'affective empathy'. 'Cognitive empathy' is viewed as being closer to ToM as a concept (Montag et al., 2007) or even equivalent to ToM (Shamay-Tsoory et al., 2007) and refers to the ability to take another perspective. Emotional or affective empathy refers to shared emotional experiences in which the ability to identify with another's emotional reaction enables the individual to be able to experience the same or a similar response (Montag et al., 2007).

Simulation theory is based on the assumption that *perceiving* the actions and emotional expressions of others uses the same neural and cognitive resources that are required for *producing* these actions and expressions in oneself (e.g. Gallese, 2001). According to this view, empathy emerges from a set of cognitive

processes involving perception and action rather than resulting from a dedicated 'empathy mechanism' (Ward, 2006). Mirror neurons – neurons with motor properties in premotor and posterior parietal cortex that fire during action and also while observing someone else performing the same or a similar action, have been proposed as playing an important role in social cognition, particularly empathy (Iaconobi, 2009).

Evidence in support of this conceptualisation of empathy comes from neuroimaging evidence that watching another person being touched activates the same neural mechanisms in somatosensory cortex as when physical touch is experienced (Keysers et al., 2004). Other neuroimaging studies have reported similar findings for expectation and experience of pain (Singer et al., 2004), as well as observation of the facial expression of disgust in others (Calder et al., 2000). What remains unclear is whether these ideas relating to empathy can be extended to account for ToM. Gallese (2003) argues that the ability to represent mental states (as required for ToM) is continuous with emotions and sensations, whereas others (Leslie, 1987; 1994) have proposed the need for a domain-specific mechanism for ToM.

Compared to the widespread research into ToM, empathy has received less attention in healthy individuals and in psychopathology. However, despite its complexities, research into empathy is increasing, with growing evidence for empathy deficits in individuals with autistic spectrum disorders (Baron-Cohen & Wheelwright, 2004; Shamay-Tsoory et al., 2002), schizophrenia (Montag et al.,

2007) as well as following pre-frontal cortex lesions (Shamay-Tsoory et al., 2003) and in frontotemporal dementia (Perry et al., 2001).

Increasingly, research is exploring whether there is evidence for separation of cognitive and affective empathy in various patient groups. In their study of two adolescent males with Asperger's syndrome, Shamay-Tsoory et al., (2002) reported impaired cognitive and affective empathy which was not associated with impaired recognition of emotion or executive function. Shamay-Tsoory et al., (2002) call on Frith's (1989) model of 'weak central coherence' to explain these findings: proposing that the empathy deficits in Asperger's Syndrome may be explained by a failure to integrate cognitive and affective components in order to respond adaptively (and empathically) in social situations. In their investigation into self-reported empathy in individuals with schizophrenia, Montag et al., (2007) reported significantly lower scores in cognitive empathy (perspective-taking), but no significant difference in ratings of affective empathy between the individuals with schizophrenia ($n = 45$) and healthy controls ($n = 45$). These findings support the possibility of differentially disturbed cognitive and affective empathy abilities in schizophrenia.

Meanwhile, comparison of cognitive and affective empathy in patients with prefrontal lesions, parietal lesions and healthy controls highlighted that those with prefrontal lesions were significantly impaired in both cognitive and affective empathy compared to parietal patients and healthy controls. Interestingly, correlations between impaired cognitive flexibility and reduced

cognitive empathy suggested a dissociation between the cognitive correlates of affective and cognitive empathy (Shamay-Tsoory et al., 2004).

1.7.4 Neuroanatomy of social cognition

Evidence for the neural basis of different aspects of social cognition has mainly come from functional imaging studies of healthy participants and behavioural studies of patients with brain lesions. The continuing advancement of neuroimaging techniques, particularly functional magnetic resonance imaging (fMRI) and diffusion tensor magnetic resonance imaging (DTI) has provided vital information about the neural substrates of different aspects of social cognition.

In terms of emotion recognition, bilateral lesions affecting the amygdala have been shown to result in selective impairment of the ability to recognise fearful facial expressions (Adolphs et al., 1994; Calder et al., 2004). Morris et al., (1996) measured regional cerebral blood flow whilst they presented five healthy participants with morphed faces on a happy-neutral-fearful continuum. Participants were required to make a male/female classification so emotion processing was incidental rather than the main focus of the test. Analysis showed left amygdala activation was found only in the fear condition. Morris et al., (1996) interpreted their results as evidence for involvement of the human amygdala in fear processing, even when explicit processing of emotional content was not required by the task demands. In terms of the neural pathways involved in facial emotion processing, the current view proposes a combination of fast, automatic, processing (e.g. a subcortical route from the thalamus to the

amygdala) and slower, controlled processing (e.g. to the amygdala via primary visual cortex) (Adolphs, 2002; 2009).

Efforts to elucidate the neural basis of ToM, have included the use of many different tests in varying modalities: including inferring mental states from stories (e.g. Fletcher et al., 1995), cartoons (e.g. Gallacher et al., 2000) and interactions with others (e.g. McCabe et al., 2001). In their meta-analysis of the functional imaging literature, Frith and Frith (2006) highlight three key areas involved in ToM. The parietotemporal junction (TPJ), temporal poles (TP) and medial prefrontal cortex (mPFC). The parietotemporal junction was activated in response to biological motion, eye gaze, moving mouths and living things in general as well as during a ToM test (Frith & Frith, 2006). In addition to processing observable actions, the idea that this region may also be involved in inferring mental states is supported by evidence from a human lesion study (Samson et al., 2004). Thus, the importance of this region for ToM abilities is emerging.

Although the temporal poles (TP) are usually activated in tests of language and semantic memory, activity in this region has also been observed during a ToM test that did not involve linguistic stimuli (where triangles that appeared to interact were used as stimuli) (Castelli et al., 2000). Consequently, Frith and Frith (2006) suggest that the TPs are involved in the generation of schemas that specify the current emotional or social context. Moriguchi and colleagues (2006) provide further evidence to support the proposition that activity in TP is associated with ToM abilities.

Medial prefrontal cortex (mPFC) was activated in all ToM tests included in Frith and Frith's (2006) meta-analysis. Activity in the mPFC has been reported when thinking about the mental states of others as well as the self (Frith & Frith, 1999). There is also evidence for segregation of function within the mPFC. For example, thinking about others perceived as similar to the participants resulted in activation of the ventral mPFC compared to more dorsal mPFC when thinking about the mental states of another person perceived to be different to the participant (Mitchell et al., 2006). Although the fine details of mPFC involvement in ToM remain to be clarified, it is clear that mPFC has an important role in the neural basis of thinking about others' states of mind.

Some studies of patients with frontal lobe injury have concluded that mPFC is necessary for ToM (e.g. Stuss et al., 2001). However, others have disagreed with this conclusion (Bird et al., 2004). Of relevance to the debate about the extent to which executive functions underlie ToM abilities are findings of Rowe and colleagues (2001) and Stone et al., (1998) who found that acquired differences in ToM were dissociated from aspects of executive function measured in their studies.

If empathic responding is characterised as including cognitive and emotional aspects, then the mechanisms mediating empathy are likely to rely on the integration of emotional and cognitive information (Shamay-Tsoory et al., 2004). A lack of evidence for specific lesions that result in impaired empathy supports the idea that several circuits may be involved in the mediation of empathy.

Important mechanisms for empathy may include mechanisms involved in ToM such as mPFC, the TPJ and TP, as discussed previously. For emotional aspects of empathy, simulation theory proposes the involvement of mirror neurons in inferior frontal and posterior parietal cortices (e.g. Iaconobi et al., 1999). Consistent with this suggestion, correlations between activation in inferior frontal cortex during empathy-related attributions and individual empathic abilities have been reported (Schulte-Ruther et al., 2007). Diminished activation in inferior frontal cortex in people with ASD during observation and imitation of facial expressions (which correlated with symptom severity) provides additional evidence for involvement of this region in empathy (Dapretto et al., 2006).

1.7.5 White matter damage/disruption and social cognition

As already discussed, white matter pathology has the potential to disrupt any aspect of cognitive function, but appears to particularly affect operations subserved by frontal-subcortical networks, such as executive control, working memory, and sustained attention (Filley, 2005). This profile of cognitive impairment has been attributed to the concentration of white matter disease in frontal white matter as well as the dense connectivity between frontal and other brain regions (Filley, 2005). Consideration of the neural basis of social cognition highlights the potential for white matter pathology to affect aspects of emotional processing (Henry et al. 2009) - particularly because social cognition appears to rely on widespread cortical networks that include frontal and temporal systems (Apperly et al., 2004; Decety & Jackson, 2004), and these long fibre tracts may be particularly susceptible to white matter disruption. The potential impact of

white matter pathology on social cognition is further highlighted by recent evidence that functional and anatomical underconnectivity has been identified in autism (Just et al., 2007).

1.8 Social participation/involvement in MS

As discussed earlier, people with MS report lower QoL compared with the general population (e.g. Norvedt et al., 1999). There appears to be a particularly negative impact on social functioning in MS (Norvedt et al., 1999). This finding is important to explore as restriction in social involvement correlates with reduced health-related quality of life (Aronson, 1997). MS may impact on social participation in a number of different ways. For instance, functional limitations, such as limited mobility and problems with bowel and bladder control may make participation in activities difficult. These types of functional limitations may also limit social participation because of associated feelings of embarrassment or shame (Halper, 2007). People with MS also report limiting their social and occupational activities as a result of experiencing MS-related fatigue (Krupp et al., 1988). People with MS may also experience social exclusion as a result of discrimination (Halper, 2007).

Whether or not people experience disability as a result of their MS, it is important to recognise the contribution of social skills to an individual's potential for successful social involvement. Indeed, for individuals with MS, effective social skills may be even more important to facilitate successful social participation as other individuals may experience anxiety about interactions with an individual with MS (Marinelli et al., 1977, cited in Halper, 2007).

Experience of relapses may also cause individuals to temporarily withdraw from social contact as they cope with the resulting physical and emotional changes they experience (Halper, 2007). It has become increasingly evident that the impact of MS on quality of life is broad (Norvedt et al., 1999) and that social participation forms an important aspect of quality of life in MS and is an important area for research and possible intervention.

1.9 Insight in MS

Given the evidence for executive impairment in MS and the links between executive function and frontal lobes systems, the issue of whether insight is affected in MS is theoretically and clinically relevant. Research into insight in MS is an emerging area in which few studies have been carried out to date. Research into issues relating to insight and awareness is complex, as although the term 'insight' is used widely, there is a lack of clarity about the meaning of this term (Bond et al., 2002). Within a medical context, insight is often conceptualised as the degree to which people express awareness about the nature and extent of deficits related to their illness (Sabat, 2002). Particularly in relation to neurological illness or injury, apparent unawareness of the impact of illness/injury is usually viewed as a direct symptom of neurological change (Clare, 2002). However, the concept of insight can also be viewed as being more complex, multi-factorial and value-laden than this definition implies (Howarth & Saper, 2003).

Insight is generally assessed through comparison of self-report to external data, such as proxy-report (data from someone who speaks for a patient because they

cannot or will not speak for themselves) and other-report (perspectives collected in addition to self-report, for example from a close relative, friend or clinician) (Snow et al., 2005). Although exploring aspects of insight by calculating the discrepancy between self-report and other-report data is the most widely-used method, it is important to note that a discrepancy between self and other-report data is not necessarily indicative of impaired insight on behalf of the patient (Snow et al., 2005). The results of investigations of aspects of insight in MS have been varied, with Benedict et al., (2001) reporting significant discrepancies between self and other-report on empathy measures, with MS patients providing higher self-ratings. Warwick (2008) found MS self-report indicated greater impairment in impulsivity and memory compared to other-ratings on the Brock Adaptive Functioning Questionnaire. Van der Linden et al., (2008) reported evidence that relatives may overestimate the impact of MS compared to people with MS themselves. Given the importance of self-report for the validity of outcome measures for MS treatment and rehabilitation, the issue of reliability of self and other ratings is an important area for further investigation.

1.10 Recent research into social cognition and executive function in MS

A recent study that integrated issues relating to white matter pathology in MS and the potential impact on social cognition and executive functioning in MS was carried out by Henry et al., (2009). In their study, 27 individuals with MS and 30 healthy controls were administered measures of facial affect recognition, a ToM test and tests of general cognitive functioning. To measure facial affect recognition, 48 black and white photographs (Ekman & Friesen, 1976) were shown and participants were asked to choose the emotion label that best

described the emotion displayed on each face. The Revised Mind in the Eyes test (Baron-Cohen et al., 2001) was used to measure ToM. Participants chose which word best described the thoughts or feelings expressed in 36 pictures of eyes. Henry et al., (2009) suggest that this test differs from basic affect recognition because the distinctions involve more complex emotional terms and social interaction. The Screening Examination for Cognitive Impairment (SECFI – Beatty et al., 1995) was used to assess cognitive function as it has been shown to be reliable and sensitive to cognitive impairment in MS (Beatty et al., 1995). The SECFI includes four cognitive measures: delayed verbal recall, vocabulary, abstraction and information processing speed. Each participant also completed measures of semantic and phonemic fluency (using the probes animals, fruits and vegetables, and F, A, S respectively).

Comparing performance of the individuals with MS with healthy controls, significant MS deficits were observed for the ToM test, phonemic fluency and SECFI short delay. On the facial recognition test there was no main effect of group but an interaction between group and emotion type. Further analysis using t-tests then showed that recognition of anger and fear were disrupted in the MS group (Henry et al., 2009). Performance on measures of facial affect recognition and ToM were related in both groups, shown by significant correlations ($r=.47$ and $r=.61$) for the control and MS groups respectively. There appears to be considerable overlap in the abilities tapped by these tests, particularly in the MS group (Henry et al., 2009). In terms of possible associations between performance on emotion understanding measures, cognitive function and mood measures, in the MS group, poor scores on verbal

fluency were significantly associated with impaired ToM performance. Processing speed was correlated with emotion recognition (Henry et al., 2009).

Henry et al., (2009) concluded that these findings demonstrate that the MS group, relative to controls, had greater difficulty detecting subtle differences in mental states from pictures of eyes. Although no overall group differences in facial affect recognition were observed, specific difficulties with recognition of anger and fear were reported in the MS group. These findings were interpreted as consistent with broader evidence suggesting that white matter pathology has the potential to disrupt not only cognitive functioning in general, but also specific social perceptual skills (Henry et al., 2009). These results also raise the possibility that MS may disrupt decoding of specific facial emotions, as has been reported in other neuropsychological conditions. This study confirmed the findings of Warwick (2008) that a group of 30 MS participants were impaired at facial affect recognition compared to the published normative data on the Facial Expression of Emotion: Stimuli and Tests (FEEST, Young et al, 2002). Across a range of affect recognition tests it was found that the MS group were also impaired at recognising specific emotions – anger, disgust, fear and sadness.

In their study, Henry et al., and (2009) were the first to demonstrate that cognitive ability correlates with aspects of emotion understanding in MS. One issue which requires further clarification, is whether impairment on the Eyes test can be considered as evidence of ToM impairment, rather than emotional processing? Although the Eyes test is frequently used as a measure of ToM, it has been argued to actually represent a test of affect recognition (e.g. Bull et al.,

2008). Further investigation of the performance of people with MS on a range of ToM tests might help clarify this issue.

A related issue, which is gaining prominence, is the possible role of empathy deficits in reduced social quality of life and social functioning, as well as exploration of possible associations between the processes involved in empathy, ToM and executive functions. As far as the author is aware, the only study which has directly measured empathy abilities in MS was carried out by Benedict et al., in 2001. They found that the MS group were rated lower on the Hogan Empathy Scale (Hogan, 1969) compared to healthy controls, and that performance on tests thought to measure executive functioning (Wisconsin Card Sorting Test, Booklet Category Test) predicted lower empathy scores. This finding has not been replicated and there are some concerns about their generalizability because the participants responded to advertisements that targeted people with MS who were experiencing “emotional problems”.

Another interesting development relating to empathy, is the apparent separation of cognitive and affective empathy abilities in individuals with schizophrenia, autism and brain injury. Shamay-Tsoory et al., (2007) report cognitive empathy as being particularly related to measurements of orbitofrontal (rather than dorsolateral) functioning whereas affective empathy was related to measures of social function. These unresolved issues relating to empathy, suggest further investigation of empathy in MS is timely and relevant.

In the context of the importance of facial recognition skills and other emotional understanding skills for the development and maintenance of interpersonal relationships, social participation and QoL, Henry et al's., (2009) observation of impaired social cognition in MS raises theoretically and clinically important issues that also deserve closer attention.

1.11 Summary and research aims

Multiple Sclerosis is a chronic, inflammatory demyelinating disease of the central nervous system, which is the most common cause of neurological disability in young adults in the UK. The impact of MS on physical abilities is well-known. There is now increasing recognition of the impact of MS on mood (particularly depression) and cognition (particularly attention, memory and executive functioning). Recently, the potential for white matter pathology to affect social cognition, such as recognition of facial expression and ToM has been highlighted. As MS is primarily a white matter disease, investigation of social cognition in MS is theoretically important and relevant. In addition, evidence from investigations into QoL in MS highlight self-reported low QoL in the domain of social participation, emphasising a possible clinical need in this group.

A recent investigation of emotion recognition, TOM and executive function in MS (Henry et al., 2009) demonstrated impaired emotion recognition and impaired TOM ability in a sample of people with MS. Significant difficulty on the TOM test (Revised Eyes test, Baron-Cohen et al., 2001) was related to level of executive impairment as measured by verbal fluency. Research into

schizophrenia, autism, traumatic brain injury and ageing has also highlighted links between TOM ability and executive function which remain to be clearly elucidated. Given the recent evidence for the impact of MS on aspects of social cognition and the potential impact of these difficulties on QoL, further detailed investigation using a range of ToM and empathy measures in a group of people with MS is timely. In addition to providing the opportunity to further explore theoretical aspects of TOM, empathy and executive functioning (and the potential links between these concepts), it is also clinically relevant because of the potential negative impact of impaired ToM, empathy and executive functioning on QoL in MS. The importance of highlighting and increasing understanding of the potential psychological and cognitive impact of MS is also of clinical significance.

1.12 Hypotheses

The following hypotheses are under investigation:

Hypothesis 1: Reduced performance on measures of executive functioning (Mental Flexibility, Inhibition and Response to Feedback) will be associated with reduced performance on Theory of Mind (ToM) tests.

In particular, there will be significant, positive correlations between performance on measures of mental flexibility, inhibition and letter fluency and ToM. There will be larger positive correlations between executive functioning and ToM performance compared to processing speed (as measured by Colour Trails Test 1 - CTT 1) and executive functioning performance.

Hypothesis 2: Reduced performance on measures of executive functioning (Mental Flexibility, Inhibition and Response to Feedback) will be associated with reduced empathy.

Positive correlations between the executive functioning measures and both the Interpersonal Reactivity Index (IRI – Davis, 1980) Perspective-Taking subscale and Empathy Quotient Questionnaire (EQ - Baron-Cohen & Wheelwright, 2004) will be higher than the correlations between the executive function measures and other IRI scales. The EQ and Perspective-Taking subscale are thought to measure more cognitive aspects of empathy.

Hypothesis 3: Reduced performance on measures of executive functioning (Mental Flexibility, Inhibition and Response to Feedback) will be associated with lower self-reported quality of life.

Executive functioning performance will be positively associated with self-report QoL ratings. In particular, there will be a stronger positive correlation between performance on executive functioning tests and the Psychological and Social subscales of the World Health Organisation Quality of Life – BREF Questionnaire (WHO QoL-BREF) (Skevington et al., 2004) compared to the Physical and Environment subscales. A stronger association between executive functioning performance and the Psychological subscale of the Multiple Sclerosis Impact Scale (MSIS-29) (Hobart et al., 2001) compared to the Physical subscale is also predicted.

Hypothesis 4: Reduced performance on measures of ToM (Revised Eyes, Videos and Stories test) will be associated with lower self-reported quality of life.

ToM performance will be positively associated with self-report QoL ratings. In particular, there will be a stronger positive correlation between performance on ToM measures and the Psychological and Social subscales of the WHO QoL-BREF compared to the Physical and Environment subscales. A stronger association between ToM performance and the Psychological subscale of the MSIS-29 compared to the Physical subscale is also predicted.

1.12.1 Additional research questions

The current study also provides the opportunity to explore the impact of MS on a range of ToM tests, potentially replicating the findings of Henry et al., (2009) and extending them by including ToM tests involving static facial expressions, dynamic scenes and stories. It also provides the opportunity to explore whether ToM and empathy are affected differently in MS for the first time. Inclusion of empathy measures rated by others means it is possible to explore whether self- and other-empathy reports differ according to the information source. Finally, the study aims to add to current knowledge about ToM, empathy, executive functioning, anxiety, depression and issues relating to quality of life in MS.

Chapter 2 Methodology

2.1 Design

This study made within-subjects repeated measures comparisons, as well as comparisons between the sample and published control data and between other- and self-report measures. The within-subjects repeated measures comparisons enabled investigation of the relationships between the dependent variables – performance on executive functioning tests, ToM tests, empathy and QoL measures. Other-rater data was collected for the empathy measures.

2.2 Participants

2.2.1 Inclusion and Exclusion Criteria for MS participants

For participants with MS, the following inclusion criteria were applied:

1. Aged between 18 and 65 years - to avoid confounding effects of developmental changes in cognitive function below the age of 18 and age-related changes beyond age 65.
2. Must meet McDonald Criteria for MS diagnosis, as defined by a Consultant Neurologist – to ensure that participants met clinically accepted MS diagnostic criteria.

Participants were excluded if they met any of the following criteria:

1. Deemed not to have capacity to consent
2. A history of neurological disease other than MS or a history of traumatic brain injury or psychiatric disorder

3. Poor understanding of English that would negatively affect their ability to complete questionnaires or understand test instructions.
4. A severe visual or aural impairment that would negatively affect their ability to satisfactorily complete tests or understand test instructions
5. Benign type of MS: as this form of MS is much less likely to be associated with cognitive impairment than other forms of MS (Rovaris et al., 2008).

Any potential participants who had previously been assessed by a healthcare practitioner and deemed not to have capacity to consent were not approached. Any potential participants who had recently been involved in other research studies or who were considered by their neurologist not to be appropriate for the study were not approached. Seven participants were excluded on the basis of these criteria.

2.2.2 Inclusion and Exclusion Criteria for Other-Rater Participants

Each participant with MS was asked to nominate someone who knew them well (for example, a close relative, spouse or friend), to act as an 'informant' participant to complete the two empathy questionnaire other ratings. Participants with MS were advised to select this individual according to the following criteria:

1. A person who knows the participant with MS well
2. A person who does not have MS or any known neurological or psychiatric condition.

3. A person who has a good understanding of English
4. A person who does not have a significant visual or aural impairment.

Other-reports were not received for ten participants who took part.

2.2.3 Demographic Information Collected

Demographic information on gender, age and estimated years of formal education was collected from MS participants.

2.2.4 MS-related Information Collected

The following MS-related information was collected from participants with MS:

1. Type of MS (Relapsing-Remitting, Primary Progressive or Secondary Progressive)
2. Length of time since MS diagnosis
3. Length of time since onset of first symptoms.

2.2.5 Recruitment

Potential participants with MS were identified by their Consultant Neurologist using the Department of Neurology's MS Patient Database at Aberdeen Royal Infirmary. A letter outlining the purpose of the research (Appendix 1) was sent to potential participants. An enclosed Information Sheet (Appendix 2) provided details about participation. A form requesting volunteers' contact details was attached to this letter. A stamped, addressed envelope was provided to enable participants to return their contact sheet.

The author telephoned those individuals who expressed an interest in the study to discuss any questions they had about the research and to clarify whether they were choosing to participate. An appointment for a 60 minute assessment was then made. Each participant was seen at either a local hospital or the local MS Resource Centre, according to their preference.

2.3 Ethical Considerations

The following ethical issues were considered.

2.3.1 Potential Distress to Participants

Although great care was taken to minimise the potential for distress to participants, it was important to acknowledge that some participants may become distressed during completion of neuropsychological assessments. All participants were reminded that they were free to withdraw at any time and that the author and/or her thesis supervisor were available to discuss any concerns.

It was also important to consider the possibility that participants with MS may become fatigued during assessment. All participants were given the option to complete the assessment during two sessions, if preferred.

A protocol was agreed in which if participation in the study did highlight a serious mood disorder or cognitive impairment which was not previously recognised and was not being addressed, the author would discuss this issue in

supervision and that the participant's neurologist would be consulted if necessary. It did not prove necessary to use this protocol.

2.3.2 Informed Consent

2.3.2.1 Informed Consent for Participants with MS

When meeting participants for the first time, it was again highlighted that they were free to withdraw at any time and that this decision would in no way affect their future involvement with the health service. The aims and process of the study was then outlined again and the participant was asked whether they still wished to participate. If they agreed, they were provided with a Consent form (Appendix 3) to read and sign.

2.3.2.2 Informed Consent for Other-rater Participants

Participants with MS were asked to consider approaching someone who knew them well to complete other-reports for the two empathy questionnaires. An information sheet was provided for these participants, which included contact details for the author and her supervisor to answer any questions. The returned questionnaires were taken as consent to participate in the study.

2.3.3 Confidentiality

The confidential nature of all information collected throughout the study was emphasised to participants in the Invitation Letter, Participant Information Sheet and during discussion. For the purpose of identification, each participant was assigned a unique number. All demographic data was then anonymised. This anonymised data was transferred onto a password-protected National

Health Service (NHS) computer. Each participant's unique identification number was the only link to their personal information. Personally identifiable data (e.g. name, date of birth, address) was stored in a locked filing cabinet on NHS premises. The key to link the personally identifiable data with participant codes was kept in a separate locked filing cabinet on NHS premises.

The author analysed the data. Data analysis took place in the author's office, using an NHS computer, on NHS premises. No personally identifiable data was stored on this computer. Data were regularly saved onto a compact disc which was stored in a locked filing cabinet in the author's office. Only the author and her supervisors had access to this data. These procedures ensured that high standards of confidentiality were maintained.

Data from the study will be kept securely on NHS premises for ten years, in accordance with current research governance guidelines, before being destroyed.

2.3.4 Ethical Approval

An application for ethical approval was submitted to NHS Grampian North of Scotland Research Ethics Committee on 9th December 2008. Written confirmation of full ethical approval was received on 27th January 2009 (Appendix 4). Following this, the study was registered with NHS Grampian's Research and Development office, who on 18th February 2009 gave their approval for the study to commence (Appendix 5). Indemnity cover was

provided by the University of Edinburgh prior to the research commencing (Appendix 6).

2.4 Statistical Power and Sample Size

Sample size estimation depends on the strength of the relationship that is being explored (effect size) and the amount of statistical power required to be able to detect such effects (Field, 2005).

The number of participants in this study was comparable to the only relevant studies reported in the literature (e.g. Henry et al., 2009; Warwick, 2008). Sample size was determined by a power analysis (using GPower3) for the main hypotheses, based on published effect sizes from experiments with similar aims.

- Hypothesis 1: Reduced performance on measures of executive functioning (Mental Flexibility, Inhibition and Response to Feedback) will be associated with reduced ToM performance. As Henry et al., (2009) reported a correlation of $r = .65$ between performance on the Eyes test and verbal fluency, the sample size required to detect a hypothesised large correlation (effect size $=0.5$) with the power of 0.8 (high) and an alpha level of 0.05 (one-tailed) is 29.
- Hypothesis 2: Reduced performance on measures of executive functioning (Mental Flexibility, Inhibition and Response to Feedback) will be associated with reduced empathy. As Shamay-Tsoory et al., (2007) reported a correlation of $r=.36$ between the Interpersonal Reactivity Index

and performance on a measure of cognitive flexibility in their sample of individuals with schizophrenia, the sample size required to detect a hypothesised moderate correlation (effect size =0.4) with the power of 0.8 (high) and an alpha level of 0.05 (one-tailed) is 34.

- Hypotheses 3 and 4: Reduced performance on measures of executive functioning (Mental Flexibility, Inhibition and Response to Feedback) and ToM (Revised Eyes, Stories and Videos) will be associated with lower self-reported quality of life. The sample size required to detect a hypothesised moderate correlation (effect size=0.4) with the power of 0.8 (high) and an alpha level of 0.05 is 34.
- Additional Research Question: To ascertain whether empathy reports varied according to the information source (self or other-report) based on the effect size of 0.7 reported by Warwick (2008) in a sample of individuals with MS and other-rater participants, the sample size required to detect such an effect with the power of 0.8 (high) and an alpha level of 0.05 (one-tailed) is 13.
- Additional Research Question: To explore cognitive empathy (ToM) and affective empathy were affected differently in MS a two-tailed analysis was required. The sample size required to detect a hypothesised moderate correlation (effect size=0.4) with the power of 0.8 (high) and an alpha level of 0.05 is 44.

Having data from 42 MS participants and 32 other-rater participants in the final analysis ensured that the study had sufficient power to detect relationships between variables should they exist in this sample.

2.5 Analysis

The main aims of this study were to investigate the relationship between performance on measures of specific executive function abilities (Mental Flexibility, Inhibition and Response to Feedback), and both ToM performance and empathy in an MS sample. A secondary aim was to determine whether performance on executive function tests, ToM and empathy measures have a stronger association with Social and Psychological QoL than Physical QoL in MS.

Data was analysed using a statistical software package developed for the social sciences (SPSS for Windows, Version 17).

2.5.1 Exploratory Data Analysis

Exploratory data analysis was conducted to ensure that the assumptions for appropriate use of parametric statistics were met (Gravetter & Wallnau, 1996). To check whether the data was normally distributed, a frequency distribution was used to plot the data and to check for the presence of outliers. Together with visual inspection of distributions, non-significant values ($p > .05$) in the Kolmogorov-Smirnov test were taken to indicate that the distribution of the sample was not significantly different to normal. To test for homogeneity of

variance, visual inspections of scatterplots and Levene's test ($p > .05$) were taken as indicating homogeneity of variance.

2.5.2 Correlational Analysis

Pearson's product moment correlation coefficients were completed between raw scores to establish relationships between executive functioning test performance, ToM test performance, empathy ratings and quality of life. In addition to calculating the correlation coefficients between individual EF and ToM measures, the association between composite EF and ToM measures was also examined.

Bonferroni Corrections were used to adjust the critical significance value when a large number of correlations were completed to reduce the risk of Type 1 errors.

2.5.3 Analysis for Additional Research Questions

2.5.3.1 Comparison to Normative Data

A score of one standard deviation (1SD) or more below the normative mean was used to classify performance as potentially impaired compared to data from healthy participants. This criterion had the advantage of being sensitive to possible deficits, although it was important to consider that approximately 16% of the normal population would be expected to score within this range (Lezak et al., 2004).

2.5.3.2 Comparison of Self-Report and Other-Report on Empathy Measures

Repeated-measures t-tests were completed to determine whether there were significant differences in the self and other empathy reports.

2.6 Measures

2.6.1 Order of Measures

During the assessment appointment, the consent form was first completed, followed by the Background Information Sheet, Hospital Anxiety and Depression Scale (Zigmond & Snaith, 1983) and Disease Steps (Hohol et al., 1995).

Participants then completed the ToM and neuropsychological assessment measures. Presentation order was counterbalanced to spread the potential impact of fatigue across the different measures in the study.

The ToM tests were the Revised Eyes Test (Baron-Cohen et al., 2001), Videos Test and Stories Test (Slessor et al., 2007). The Neuropsychological assessment measures were the National Adult Reading Test (NART) (Nelson, 1982), Colour Trails Test I (D'Elia et al., 1996), Hayling Sentence Completion Test (Burgess & Shallice, 1997), Brixton Spatial Awareness Test (Burgess & Shallice, 1997) and the Controlled Oral Word Association Test (COWAT, a measure of verbal fluency) (Benton & Hamsher, 1989).

Participants were then given four questionnaires to complete immediately or at home and return by post (using the postage-paid envelope provided). These

were the Empathy Quotient Questionnaire (EQ - Baron-Cohen & Wheelwright, 2004), the Interpersonal Reactivity Index (IRI - Davis, 1980), the World Health Organisation Quality of Life brief questionnaire (WHO QoL-BREF - Skevington et al., 2004) and the Multiple Sclerosis Impact Scale (MSIS-29 - Hobart et al., 2001).

In total, MS participants completed 12 measures, each of which is outlined below.

Other-rater participants were asked to complete the two empathy questionnaires - EQ and IRI. This process enabled the informants' perceptions of the people with MS (who nominated them) to be examined.

2.6.2 Demographic Characteristics

A brief background information sheet (Appendix 7) recorded participants' gender, age, estimated years of education and current occupation, or previous employment.

2.6.3 Theory of Mind (ToM) Measures

As Theory of Mind (ToM) refers to the ability to represent mental states such as the beliefs, thoughts and intentions of others (Maylor et al., 2002), tests assessing ToM focus on the ability of participants to decode these factors from a range of stimuli. As different ToM measures might be differentially affected by neurological change, it is important to measure a range of ToM abilities (Saltzman et al., 2000).

The following ToM measures were administered to participants, following the procedure described by Slessor et al., (2007). The ToM measures were computerised tests, each including a control test (to distinguish whether impaired performance on ToM tests reflected specific failures to decode the mental states of others or more general difficulties with task demands). The order in which the different ToM and control tests were presented was counterbalanced. In addition to verbal and written instructions, one practice item preceded each test to familiarise participants with test demands. Participants responded verbally and the author wrote down their response immediately.

The Revised Eyes, Videos and Stories Tests were chosen as the ToM outcome measures for several reasons. The Revised Eyes Test has been widely used as a measure of ToM in clinical and healthy populations. To extend the findings of Henry et al., (2009) this study included tests of other aspects of ToM. Given the evidence for impaired facial affect recognition in MS (Henry et al., 2009; Warwick, 2008) inclusion of a non-pictorial measure of ToM was relevant.

These ToM tests had the advantage of minimising working memory load as the response options were presented on the screen throughout. However, the Videos test did potentially involve aspects of working memory as the stimulus was transitory. The Videos and Stories tests have not been used in an MS population previously, so the current study provided new information on ToM

performance in MS. However the lack of normative data remains a limitation to the use of these tests.

2.6.3.1 Revised Eyes Test (Baron-Cohen et al., 2001)

The Revised Eyes test (Baron-Cohen et al., 2001) (referred to as 'Eyes test') was originally developed to detect and measure subtle impairment in social understanding in adults with autism and Asperger's syndrome. It is a revised version of the earlier "Reading the Mind in the Eyes" Test (Baron-Cohen et al., 1997). The Eyes test consists of 25 black-and-white photographs of the eye region. These are surrounded by four words, one target and three foils, describing complex mental states such as *annoyed*, *hostile*, *horrified* and *preoccupied*. Participants were asked to identify which word best described the mental state of the person. The control eyes test used the same stimuli but required participants to judge the age and gender of the target person by choosing the option that best described the age and gender (e.g. *Male 40-50*, *Female 40-50*, *Female 50-60*, *Male 50-60*).

Successful performance on the Eyes test is thought to rely on conceptualisation of another's mental states, and the ability to attribute these and emotions to others (Baron-Cohen et al., 1997). Baron-Cohen and colleagues recognise that the Eyes test only involves the first stage of attribution of ToM as participants are required to identify what the person in the picture is thinking or feeling (e.g. compassion), but are not required to make the second stage of attribution (e.g. compassion for her mother's loss). Some researchers (e.g. Bull et al., 2008) have

conceptualised the Eyes test as essentially being a test of emotion recognition (Bull et al., 2008).

The normative data for the Eyes test (Baron-Cohen et al., 2001) was based on healthy volunteer data from a study which compared a group of adults (n=15) with either Asperger's Syndrome (AS) or High-Functioning Autism (HFA) with healthy volunteers (n=239). This study reported that the test successfully discriminated between the participants with AS or HFA and the healthy controls. Importantly, it has previously been demonstrated that adults with AS or HFA who showed impaired performance on the Eyes test, were not significantly impaired on a control gender recognition test (Baron-Cohen et al., 1997). Clinical use of the Eyes test has revealed impaired performance on the Eyes test in a group (n=5) of individuals with bilateral orbito-frontal lesions (Stone et al., 1998). However, the performance of individuals (n=5) with left dorsolateral prefrontal damage was not significantly different to controls. More recently, Hamilton et al., (in preparation) reported impaired performance on the Eyes test in a group (n=15) of patients with right hemisphere damage following stroke.

The Eyes test was included in the test battery as it is a widely-used measure of ToM, which is relatively quick to administer. Furthermore, because the response options are presented on the screen during the test itself cognitive load is reduced.

2.6.3.2 Videos Test (Slessor et al., 2007)

The Videos Test was adapted by Slessor et al., (2007) from the ToM Videos Test devised by Sullivan and Ruffman (2004). It consists of 16 silent 5 second colour video clips showing characters interacting. Participants are instructed to choose the word that best describes the thoughts or feelings of the person in the video. It is clear from the angle of filming, which character participants are being asked to judge. Each clip is surrounded by four possible options describing mental states such as *frustrated*, *excited*, *annoyed* and *bored*. Incorrect response options were generated from free responses by young adults viewing the video clips during pilot testing (Slessor et al., 2007). A Control Videos Test using the same stimuli is also administered in which participants choose the option that best described the age and gender of the main participant (response choices were similar to those used for the Eyes test). In both tests, to reduce memory load, the options were presented before, during, and after the video clip.

2.6.3.3 Stories Test (Slessor et al., 2007)

The Stories Test (Slessor et al., 2007) is a multiple-choice test consisting of 12 ToM stories, which include double bluffs, mistakes and white lies (based on stimuli from Channon and Crawford (2000); Happe et al., (1998); and Stone et al., 1998). Each story was followed by a question regarding the intentions of the person in the story and four possible response options labelled A-D. Twelve control stories were also administered. These control stories had similar properties but did not include a ToM component, instead requiring general inferences, for example, about physical or mechanical causation (based on stimuli by Happe et al., 1998 and Stone et al., 1998). To reduce memory load the

passage, question and response options were all presented on the screen at the same time, where they remained until the participant had responded (Slessor et al., 2007).

2.6.4 Neuropsychological Assessment Measures

2.6.4.1 National Adult Reading Test (NART) (Nelson, 1982)

The National Adult Reading Test (NART) (Nelson, 1982) is an oral word reading test consisting of 50 words which have irregular pronunciation (e.g. chord). The purpose of the NART is to provide an estimate of premorbid intelligence. Performance is determined according to the number of pronunciation errors, with high scores indicating poorer test performance. The NART test sheet (Appendix 8) was placed at a comfortable distance from each participant and they were asked to read the words aloud. Each participant's score was obtained by checking their responses for pronunciation errors.

In terms of construct validity, Nelson (1982) examined whether NART performance could be used as a valid predictor of intelligence as assessed by a shortened version of the Weschler Adult Intelligence Scale (WAIS). The NART successfully predicted 55, 60 and 32 percent of the variance in the WAIS Full Scale (FSIQ), Verbal (VIQ) and Performance IQ (PIQ) respectively (n=120). A later study (Crawford et al., 1989) supported these findings. Overall, although poor at predicting performance IQ, the results suggest that NART performance is a useful predictor of verbal intelligence in healthy individuals.

Support for use of the NART as a valid measure of intelligence comes from a more recent study in which Crawford et al., (2001) followed up 179 individuals who had taken a 'mental ability' (IQ) test at the age of 11. A correlation of 0.73 between scores at age 11 and NART scores at the age of 77 was found. This result, in conjunction with other retrospective studies (Carswell et al., 1997) indicates that the NART is good predictor of premorbid intelligence.

In terms of reliability, Nelson (1982) reported a split-half reliability of .93 for the NART based on her standardisation sample. Similarly, Crawford et al., (1988) reported a split-half reliability of .90 in their sample of 121 healthy participants: suggesting that the NART has a high degree of internal consistency. The NART has also been found to demonstrate high levels of test-retest reliability ($r=.98$) and high inter-rater reliability ($r=.88$) (Crawford et al., 1989) provides further evidence that the NART is a very reliable measure.

As the purpose of the NART is to provide an estimate of previous ability, it is vital that the NART is resistant to the effects of psychiatric and neurological disorder (Crawford et al., 2001). Reported evidence (e.g. Crawford et al., 1992) suggests that the NART appears to be an appropriate method to estimate premorbid intelligence in some organic conditions, but not others. Accordingly, O'Carroll (1995) recommends that the NART is used as a premorbid measure only if it has been found to be insensitive to the clinical condition being investigated. In relation to MS specifically, the North American version of the NART (NART-R) has been found to be a valid measure of premorbid estimated intelligence in Relapsing/Remitting MS, but not in Progressive MS (Friend &

Grattan, 1998). Individuals with Progressive MS obtained significantly lower scores than control participants and those with Relapsing/Remitting MS.

2.6.4.2 Executive Function Measures

For the purposes of the current study, the following neuropsychological assessments were included with the assumption that they were primarily tapping the following executive functions:

- (i) Letter Fluency - Mental Flexibility
- (ii) Hayling Test - Inhibition
- (iii) Brixton Test – Uncovering Rules and Response to Feedback (referred to as 'Response to Feedback').

2.6.4.2.1 Controlled Oral Word Association Test (COWAT) – (FAS)

Measures of verbal fluency are one of the most widely used neuropsychological assessments and have been shown to be particularly sensitive to disorders involving the frontal lobes (e.g. Henry & Crawford, 2004). The most common verbal fluency test involves three trials of letter/phonemic fluency and one trial of category/semantic fluency. The letter fluency stimuli used in this study were 'F-A-S' and the category cue was 'animals'. The letters were selected on the basis of their frequency in the English language (Lezak et al., 2004), with words beginning with 'F' having a relatively high frequency, 'A' having a lower frequency and 'S' having the lowest frequency. To administer the letter fluency trials, the participant is asked to name as many words as possible that begin with the given letter of the alphabet (excluding proper nouns, numbers and the same word with a different suffix). The score is the number of acceptable words produced in three, one-minute trials (i.e. one minute per letter). The score is then

adjusted for age, gender and education (Gladsjo et al., 1999). For the category fluency trial, participants were asked to name as many animals as they could think of, beginning with any letter of the alphabet, during one minute. The category fluency score is the total number of animals named, which is then adjusted for age, gender and education (Gladsjo et al., 1999).

The sample used in the development and validation of the normative data consisted of 768 healthy adult volunteers (Gladsjo et al., 1999). Participants ranged in age from 20 to 101 years ($M = 50.4$ years, $SD = 19.4$). The influence of demographic variables on letter and category fluency was assessed in a sample of 403 individuals. Multiple regression analyses revealed that age, education and ethnicity together were significant predictors of letter and category fluency. Correlational analyses and ANOVA's demonstrated that the T-score conversions removed all or most demographic biases from the sample (Gladsjo et al., 1999).

Verbal fluency tests provide a way of quickly demonstrating whether and how well participants organise their thinking. Successful performance on this test requires the ability to organise verbal responses into meaningful groups. Short term memory is also indirectly involved in order to keep track of the words which have already been produced (Lezak et al., 2004). Reduced verbal fluency is thought to reflect impaired mental flexibility and difficulty shifting set (between letters), both of which are considered to be important aspects of executive functioning (Baldo & Shimamura, 1998).

A meta-analytic review carried out by Henry and Crawford (2004) involving 31 studies with a total of 1791 participants examined the sensitivity of tests of verbal fluency to the presence of focal cortical lesions. Compared to healthy controls, participants with focal frontal injuries had large and comparable deficits on letter ($r=.52$) and category ($r = .54$) fluency, supporting the validity of letter and category fluency as measures of frontal-executive functioning. They also concluded that letter fluency was more sensitive to frontal dysfunction than the Wisconsin Card Sorting Test. Deficits on letter fluency tests have also been shown to be associated with left temporal lobe epilepsy (N'Kaoua et al., 2001) and Multiple Sclerosis (Henry & Beatty, 2006). Further evidence supporting the view that verbal fluency provides a valid measure of frontal-executive function comes from imaging studies in which verbal fluency performance was associated with increased neuronal activation in the frontal lobes (e.g. PET - Ravnkilde et al., 2002; fMRI – Schlosser et al., 1998).

In terms of test-retest reliability, Vlaar & Wade (2003) examined letter fluency in a group of 35 people with MS, reporting good test-retest reliability ($r=.85$) and good inter-rater reliability ($r=.90$), concluding that letter fluency testing is reliable in people with MS.

Overall, the combined evidence suggests that verbal fluency can be considered a valid and reliable measure of frontal-executive functioning, specifically mental flexibility and set-shifting. Furthermore, the relatively short administration time makes verbal fluency a practical test to include in the assessment battery.

2.6.4.2.2 Hayling Sentence Completion Test (Burgess & Shallice, 1996)

The Hayling Sentence Completion Test (Burgess & Shallice, 1996) is specifically designed to measure three abilities relating to executive function: simple response initiation, inhibition of prepotent responses, and the efficiency and speed with which responses are produced (Appendix 9). The test is also thought to provide a measure of strategic thinking (Burgess & Shallice, 1996). There are two sections to the test, both comprising 15 sentences in which the last word is missing. For example, 'The old house will be torn'. In section 1, the researcher reads aloud each sentence to the participant, who is asked to verbally produce a word that sensibly completes each sentence (for example, the word 'down' would sensibly complete the sentence given above). Participants are requested to produce the word as quickly as possible. The time taken to produce an answer on each sentence is summed as the outcome measure for Section 1, providing a measure of initiation and response speed (Burgess & Shallice, 1997).

In Section 2, participants are read a series of 15 different sentences, only this time they are asked to produce a word that is completely unconnected to the sentence context. For example, 'The dough was put in the hot...(participant says)...song'. In order to successfully complete this test, participants are required to inhibit or suppress a strongly activated prepotent response (in this case 'oven') before generating a new, unconnected response (in this example 'song'). Section 2 provides two scores: total error score and response speed. Category A errors consist of those responses that could sensibly complete the sentence. Category B errors are those responses which were somewhat, but not directly, connected to the sentence. Burgess & Shallice's (1997) scoring criteria

was used to categorise responses. Participant performance on all measures was combined to provide an overall measure of response inhibition. The Hayling test was administered according to standardised instructions.

Burgess and Shallice (1997) provide normative data for the Hayling test based on a sample of 118 healthy volunteers with no documented history of psychiatric or neurological disorder. The authors excluded low NART performers (predicted verbal IQ not specified) from the standardisation sample because of “greater variability” in their performance and because of a high level of overlap between their score distribution and those of a patient sample. As a result, the standardisation sample is not representative of the general adult population in terms of predicted IQ (Mean = 116; SD = 11.5), potentially limiting the use of the Hayling test in clinical populations with lower IQs.

To support their claim that the Hayling is sensitive to frontal damage and is a valid measure of frontal-executive functioning, Burgess and Shallice (1997) compared the performance of a group of 71 healthy control participants with 47 patients with lesions of frontal cortex (‘anterior’ cases) and 27 ‘posterior’ cases, patients with lesions elsewhere in the cortex (groups were matched for estimated premorbid ability). Significant differences were reported between groups on all Hayling measures ($p < .001$). Post-hoc group comparisons revealed that the anterior group performed significantly poorer than controls on all Hayling measures ($p < .001$) and significantly poorer than the posterior group on three out of four measures ($p < .001$) (response time on section 1 just failed to

reach significance). These findings support the claim that the Hayling is sensitive to frontal dysfunction.

Further support for the Hayling as a measure of frontal-executive functioning comes from functional imaging research, which provides evidence for involvement of the prefrontal cortex in suppression of distracting information and word generation (e.g. Allen et al., 2008; Nathaniel-James & Frith, 2002). However, based on their PET study of people with Alzheimer's disease, Collette et al., (2002) highlight that inhibitory processes may also be affected by disconnections between anterior and posterior cerebral areas. This suggests that brain areas other than the frontal lobes may also be involved in performing the Hayling.

Some evidence for the convergent validity of the Hayling as a measure of executive function comes from examples of correlations between performance on the Hayling and other measures of executive functioning. Hayling error score has been reported to correlate with performance on the Six Elements Test ($r = .40$, $p < .001$) (Clark et al., 2000) and initiation time on the Tower of London test ($r = .40$, $p < .001$) (Andres & Van der Linden, 2000).

Test-retest reliability was assessed in 31 healthy volunteers retested between two days and four weeks after initial assessment. Reported reliabilities suggest the test-retest reliability of the Hayling overall score is adequate (0.76, $p < .001$ for overall score). As far as the author is aware, no test-retest reliability estimates have been reported in clinical populations, including MS. Reported

inter-rater reliability values vary from 96 per cent (Belleville et al., 2006) to 75.5 per cent (Andres & Van der Linden, 2000). Overall, these results suggest that the Hayling test has adequate reliability.

Hayling test performance has been found to correlate significantly with age and NART estimated IQ (Burgess & Shallice, 1997), suggesting that these variables may influence performance. Consequently, it was important to control for effects of age and IQ on Hayling test performance in the current study.

2.6.4.2.3 Brixton Spatial Anticipation Test (Burgess & Shallice, 1996)

The Brixton Spatial Anticipation Test (Burgess & Shallice, 1997) is a test of executive function involving concept formation or rule attainment (Appendix 10). It was specifically designed to assess ability to discover and apply logical rules, as well as assessing response flexibility to changing rules. The Brixton consists of a 56-page stimulus booklet: each page showing the same array of ten circles set in two rows of five, with each circle numbered from one to ten. On each page, one of the circles is coloured blue. The position of this circle changes (on most presentations) from page to page. The participant is shown one page at a time, and is asked to decide where the blue circle will be positioned next, by trying to see a pattern or rule based on what they have already seen on previous pages. Rules that enable accurate prediction emerge and then repeatedly change. Each response is scored as correct or incorrect. The total number of errors provides the raw test score, with a high score indicating poor performance. The Brixton test was administered according to standard instructions (Burgess & Shallice, 1997).

Burgess and Shallice (1996) describe three broad types of error on the Brixton test; perseveration (repeating one's response); misapplication of a strategy; or 'guessing'/'bizarre responses'. Consequently, it seems that the Brixton not only measures a person's ability to detect and follow a rule but may also highlight tendencies towards behaviour which is considered characteristic of dysexecutive syndrome.

The Brixton test was specifically designed to assess the performance of patients with frontal lobe damage on a rule detection test. When 77 patients with frontal lobe lesions were tested, they made more errors on this test than patients with posterior lesions and were more likely to guess or to produce 'bizarre responses' during this test (Burgess & Shallice, 1997). Individuals with frontal lesions performed significantly poorer compared to those with posterior lesions ($p < .001$). There was no significant difference in performance between those with posterior lesions and healthy controls. These results suggest that the Brixton is sensitive to frontal damage.

In terms of convergent validity, in a sample of participants with eating disorders, Tchanturia et al., (2004) reported that participants' Brixton error score loaded on the same factor as the Trail Making Test B. Consistent with this finding, de Frias et al., (2006) reported highly significant correlations between the error score of healthy older adults on the Brixton and CTT 2 ($p < .001$).

Test-retest reliability was examined for 31 healthy control participants retested at two days, one week or four weeks after initial testing. Overall test-retest reliability was 0.71, which the authors argue compares well with that obtained for Raven's Matrices ($r = .60$), a well-established test of general intelligence administered to the same group of participants.

Performance on the Brixton Test has been shown to correlate significantly with variables such as age and NART estimated premorbid IQ (Burgess & Shallice, 1997) suggesting that these variables may influence performance. These findings are supported by a number of other studies which have examined the effect of demographic characteristics on the Brixton (e.g. Andres & Van der Linden, 2000; Bielak et al., 2006; de Frias et al., 2006).

Overall, there is sufficient evidence supporting the validity and reliability of the Brixton test as a measure of executive function, specifically concept formation and mental flexibility (response to feedback). The Brixton also has the advantage of being relatively quick and straightforward to administer and score.

2.6.4.3 Processing Speed: Colour Trails Test I (D'Elia et al., 1996)

The Colour Trails Test (CTT) (D'Elia et al., 1996) was devised as a culturally unbiased version of the Trail Making Test (TMT) (originally part of the Army Individual Test Battery, 1944) (Appendix 11). The CTT was included in the current study as a measure of speed of information processing, important as slowed processing speed is a frequent consequence of MS (Calabrese, 2006). The CTT is based on coloured circles (either pink or yellow) which are numbered. In

CTT Part 1 participants are asked to draw a line connecting each circle in ascending numerical order, as quickly as they can while remaining accurate. CTT 1 provides a measure of processing speed, visual scanning, visuomotor tracking and motor speed (Lezak et al., 2004). The time taken to complete the test, number of errors and number of near misses provide the outcome score. The CTT 1 was administered according to standardised instructions.

D' Elia et al., (1996) claim that the CTT offers several advantages compared to the TMT. They highlight reduced language demands, the reduction in cultural bias, improved sensitivity to neurological changes and improved reliability. Normative data from 1528 healthy participants is provided (D' Elia et al., 1996). The average age of the sample was 57 years (SD=20.7 years), with an average of 14.1 years of education (SD=3.5 years). Although only 12 percent of the normative sample were female, D' Elia et al., (1996) argue that as gender accounted for less than 2.4 percent of the variance for performance on CTT, the relatively small proportion of females in the normative sample does not threaten the validity or utility of the CTT.

To support their claim that the CTT is a measure of possible neurological damage (particularly frontal lobe function), D'Elia et al., (1996) compared the performance of individuals (n=63) with previous traumatic brain injury (TBI) and healthy volunteers (n=63) matched to the TBI sample on the basis of age, education, ethnicity and gender. Individuals with previous TBI performed significantly more slowly on the CTT 1 and 2 compared to healthy controls (CTT 1 $p<.001$, CTT 2 $p<.01$). As the CTT 2 is assumed to tap executive skills in

addition to the information processing demands of CTT 1, it is perhaps somewhat unexpected that there was not a larger difference between performance of the TBI group and controls on the CTT 2. The CTT 2 has been criticised for not being equivalent to TMT B and for being as much a measure of visual scanning and susceptibility to visual distracters as of cognitive flexibility (Dugbarty et al., 2000).

In terms of convergent validity, D'Elia et al., (1996) refer to the study of Maj et al., (1993) which compared the performance of a sample of healthy volunteers ($n=30$) on the CTT and the TMT. Correlations between scores on the CTT1 and TMT Part A and between CTT2 and TMT Part B were both significant ($r=.41$, $p<.05$ and $r=.49$, $p<.01$ respectively), however, not particularly strong given that both assessments are purported to measure the same abilities.

The test-retest reliability of the CTT was examined by administering the CTT on two separate occasions an average of 14 days apart in 27 healthy volunteers (D'Elia et al., 1996). The test-retest reliability coefficient for CTT 1 was $r=.64$ ($p<.001$). In terms of clinical agreement ('normal' or 'abnormal' classification), there was 100 percent agreement for both parts of the CTT. However, the test-retest reliability was only calculated over a relatively short period of time and in a relatively small sample of healthy participants.

2.6.5 Self-Report Questionnaire Measures

2.6.5.1 Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1982)

The Hospital Anxiety and Depression Scale (HADS) is a brief 14-item measure developed by Zigmond and Snaith (1983, 1994) to detect the presence of anxiety and depression in patients in general medical outpatient settings (Appendix 12). It consists of two 7-item subscales designed to measure anxiety and depression. Respondents are asked to read each item and indicate (using a 4-point Likert scale) the extent to which they have felt that way during the previous week. Item scores range from 0 to 3. The authors recommend that HADS anxiety and depression subscale scores between 0-7 are classified as 'Normal', between 8-10 as 'Mild', between 11-15 as 'Moderate', and scores ranging from 16-21 as 'Severe'. However, Crawford and colleagues (2001) found that using a cut-off score of 8 resulted in a large proportion of the normal population being classified as falling within the clinical range for anxiety or depression. Consequently, they recommend adopting a cut-off score of 11 to indicate a clinical 'case' of anxiety or depression. For the current study, a score of 11 or more was interpreted as indicating clinically significant levels of anxiety or depression symptoms (following Crawford et al., 2001), with the ranges described by Zigmond and Snaith (1983) being used to classify 'moderate' and 'severe' cases.

The HADS is routinely used in clinical and research settings. In a review of 747 published research papers that used the HADS, Bjelland et al., (2002) reported good levels of internal consistency (mean Cronbach's alpha for HADS-A=.83,

HADS-D=.82), high levels of sensitivity and specificity (.80) and correlations with other self-report mood questionnaires ranging from .49 to .83. This finding suggests that the concurrent validity of the HADS is good to very good. In their normative data (n=1792), Crawford and colleagues (2001) reported high levels of internal consistency (Cronbach's alpha HADS-A=.82, HADS-D=.77, both scales=.86) and demonstrated that demographic variables had relatively little influence on HADS scores. The HADS is particularly appropriate for use in research involving participants with medical conditions as it was specifically designed to exclude items involving symptoms of anxiety or depression likely to have a physical basis.

2.6.5.2 Disease Steps (Hohol et al., 1995)

The Disease Steps Questionnaire was specifically designed to assess disease progression and disability in MS (Appendix 13). Hohol and colleagues (1995) noted that other clinical scales in MS were often complicated to administer (frequently requiring trained neurologists for administration), had low inter-rater reliability and were insensitive to disease progression. The Disease Steps Scale consists of eight classifications: 0='Normal', 1='Mild Disability, mild symptoms or signs', 2= 'Moderate disability, visible abnormality of gait', 3='Early cane, intermittent use of cane', 4='Late cane, cane-dependent', 5='Bilateral support', 6='Confined to wheelchair' and U=Unclassifiable. Hohol and colleagues (1995) reported that raters could quickly categorise the standardisation sample of 1323 patients with MS using Disease Steps.

For a sample of 60 patients, inter-rater reliability for Disease Steps was excellent ($\kappa=.8$) compared to a moderate result for the Expanded Disability Status Scale (EDSS) ($\kappa=.54$). A longitudinal study ($n=804$) which compared Disease Steps and EDSS for evaluation of disease progression found that the two scales provided similar evaluations and correlated strongly with each other. These findings support the use of Disease Steps as a simple, practical tool for evaluation of disease progression in MS (Hohol et al., 1999).

2.6.5.3 Empathy Quotient Questionnaire (Baron-Cohen & Wheelwright, 2004)

Baron-Cohen and Wheelwright (2004) developed the Empathy Quotient Questionnaire (EQ) (Appendix 14). A principal aim was to develop a more specific measure of empathy than previous instruments, which was designed for use with clinical populations. They argued that existing empathy measures were designed for use with healthy adults and frequently tap other factors. For example, the Chapin Social Insight Test (Chapin, 1942) involves choosing an effective course of action so consequently may involve knowledge of social rules *and* cultural convention (Baron-Cohen & Wheelwright, 2004). Another widely used measure of empathy, the Empathy Scale (Hogan, 1969) has been found to have four relatively uncorrelated factors: social self-confidence, even-temperedness, sensitivity and nonconformity (Johnson et al., 1983), of which only sensitivity appears to be directly relevant to empathy (Davis, 1994). Consequently, this measure may be more accurately thought of as a measure of social skill (Davis, 1994).

It terms of its design, the EQ is a self-report scale comprising 40 statements relating to empathy. Originally the EQ comprised 60 questions and included 20 'filler' questions to distract participants from the focus on empathy. However, these additional questions did not significantly alter performance and were removed to reduce administration time. In order to ensure that the chosen 40 items did reflect empathy, a panel of six experimental psychologists rated whether each of the items related to empathy as defined "Empathy is the drive or ability to attribute mental states to another person/animal, and entails an appropriate affective response in the observer to the other person's mental state". All 40 items were rated as related to empathy with all 20 filler times rated as unrelated by five out of six judges (Baron-Cohen & Wheelwright, 2004).

The participant is asked to read each of the statements and rate how strongly they agree or disagree with them on a four-point scale (1=strongly agree, 2=slightly agree, 3=slightly disagree, 4=strongly disagree). Each item scores zero if the respondent does not rate the empathic behaviour, one point if the empathic behaviour is rated mildly (i.e. slightly agree/ slightly disagree) or two points if it is rated strongly. This criteria results in a maximum score of 80 and minimum of zero, with higher scores indicating greater empathy abilities. The authors recommend a cut-off score of 30 to indicate impaired empathy. Approximately half of the items were designed to produce a 'disagree' response and half to produce an 'agree' response, to avoid response bias.

Baron-Cohen and Wheelwright (2004) report that 90 adults with Asperger Syndrome (AS) or High-Functioning Autism (HFA), who are reported clinically to have difficulties with empathy, scored significantly lower ($p < .001$) on the EQ compared to healthy, age-matched controls ($n=90$). Of the adults with AS/HFA, 81 percent scored at or below the cut-off score of 30, compared to only 12 percent of controls. This result supported the authors' assertion that the EQ is sensitive to deficits in empathy. Analysis of the EQ has also demonstrated a gender difference in empathy, with females scoring significantly higher than men, in agreement with previous research (e.g. Davis, 1980). The validity of the EQ as an empathy measure is supported by the inverse correlation ($r = -.56$, $p < .0001$) between EQ score and score on the Autism Spectrum Quotient (Baron-Cohen & Wheelwright, 2004). Furthermore, a strong positive correlation ($r = .59$, $p < .001$) between the EQ and Friendship Quotient (which assesses empathy in the context of close relationships) also supports the validity of the EQ as an empathy measure (Baron-Cohen & Wheelwright, 2004). Principal component factor analysis performed on the EQ revealed three factors: 'cognitive empathy', 'affective empathy' and 'social skills' (Lawrence et al., 2004). A significant correlation between performance on The Eyes test and the factor scores for 'social skills' was reported ($r = .27$, $p < .05$). The relationship between the EQ and IRI was also explored. Reasonable concurrent validity was shown by moderate correlations between the EQ and the 'empathic concern' ($r = .42$, $p < .05$) and 'perspective-taking' ($r = .48$, $p < .01$) subscales of the IRI (Lawrence et al., 2004). High test-retest reliability of the EQ after one year was also reported ($n=25$, $r = .83$, $p < .0001$) (Lawrence et al., 2004). In addition to the generally good psychometric characteristics of the EQ, its forced-choice format, relatively short

administration time and simple scoring (which requires no interpretation), support its use as a practical measure of empathy. Further research is required to clarify the appropriateness of using the EQ in the general population, in particular in relation to the detection of subtle empathy deficits.

2.6.5.4 Interpersonal Reactivity Index (Davis, 1980)

The Interpersonal Reactivity Index (IRI) (Davis, 1980) was developed as a multidimensional measure of empathy, which aimed to capture both cognitive (e.g. perspective-taking) and affective (e.g. emotional reactions) aspects of empathy in an instrument that was easy to administer and score (Appendix 15). The IRI was developed from a pool of 50 items. A group of 452 healthy participants responded to these items on a five-point scale (with ratings ranging from 0='does not describe me well' to 4='describes me very well'). Factor analysis revealed four main factors: fantasy items - a tendency to identify strongly with fictional characters in books, plays etc: perspective-taking items - tendency or ability to adopt the point of view of another person: empathic concern items – tendency to experience warmth, compassion and concern for others: and personal distress items - experience of feelings of discomfort and anxiety when witnessing distressing experiences of others (Davis, 1980). After exploring the psychometric properties of a 45-item version, the 28 items included in the final version of the IRI were selected because they were the items which loaded most heavily (and loaded heavily) on only one factor.

The final version of the IRI consists of four seven-item subscales which measure 'perspective-taking', 'empathic concern', 'personal distress' and 'fantasy'. The psychometric properties of the IRI were examined in a standardisation sample of 1161 healthy American volunteers (Davis, 1980). This study found strong support for the four empathy subscales, good internal reliability coefficients (.70-.78) and good test-retest reliability over 60 to 75 days (males=.61 to .79, females=.62 to .81). The fantasy and perspective-taking subscales are essentially unrelated ($r=.10$), supporting Davis' (1980) assertion that the IRI provides a multidimensional measure of empathy. There was also little relationship between the two emotional subscales of 'empathic concern' and 'personal distress' (males $r=.11$, females $r=.01$). The highest correlation between subscales was the 'perspective-taking' and 'empathic concern' ($r = .33$). Overall, there is evidence to support the IRI as a reliable measure of four separate aspects of empathy. The IRI has also been used in clinical samples including people with frontotemporal dementia (Rankin et al., 2005), brain injury (Shamay-Tsoory et al., 2003) and schizophrenia (Shamay-Tsoory et al., 2007).

2.6.5.5 World Health Organisation Quality of Life Questionnaire (WHO QoL-BREF) (Skevington et al., 2004).

The World Health Organisation (WHO) defines quality of life (QoL) as 'an individual's perception of their position in life in the context of the culture and value systems in which they live, and in relation to their goals, expectations, standards and concerns' (WHO QoL, 1994). The WHO QoL-BREF was developed as a shorter version of the WHO QoL-100, a cross-culturally validated assessment of well-being (Skevington, 1999) (Appendix 16). The 26-

items selected for inclusion in the WHO QoL-BREF comprise one item from each of the 24 facets of QoL included in the WHO QoL-100, as well as one overall QoL item and one general health item. The 24 items were selected on the basis of their ability to explain a substantial proportion of variance and for their discriminant validity (Skevington et al., 2004). The WHO QoL-BREF is scored in four domains of QoL: Physical health, Psychological, Social relations and Environment. The questionnaire is self-report, administered in less than five minutes and involves rating each item on five-point Likert scales according to how the respondent felt during the past two weeks.

The psychometric properties of the WHO QoL-BREF were examined using cross-sectional data from 11830 adults in 23 countries (Skevington et al., 2004). Respondents included healthy individuals as well as individuals in primary care, hospital and rehabilitation settings for patients with physical and mental disorders. The authors conducted analysis of internal consistency, item-total correlations, discriminant validity and construct validity through confirmatory factor analysis and concluded that the WHO QoL-BREF has good to excellent reliability and performs well in tests of validity.

The WHO QoL-BREF was chosen as a brief, reliable and valid measure of quality of life which has also been used previously in an MS sample (e.g. Phillips et al., 2008). An advantage of the WHO QoL-BREF was that it measures QoL across a range of domains, important for effective and comprehensive assessment of QoL (Naughton & Shumaker, 2003).

2.6.5.6 Multiple Sclerosis Impact Scale (Hobart et al., 2001)

The Multiple Sclerosis Impact Scale (MSIS-29) (Hobart et al., 2001) was developed as an MS-specific outcome measure which includes patient views and has rigorous psychometric characteristics (Appendix 17). To develop the questionnaire, a pool of 129 questionnaire items was generated through interviews with 30 individuals with MS, findings from a literature review and expert opinion. The questionnaire was administered by postal survey to 1530 people selected randomly from the UK MS society database. Redundant items and those with limited measurement properties were removed before the remaining 41-items were grouped into scales using factor analysis. The final MSIS-29 consists of 20 items measuring physical aspects and nine items measuring psychological aspects relating to the impact of MS. Respondents answer items on the basis of how much their MS has impacted on their day-to-day life during the past two weeks, using a five-point Likert scale (1=Not at all, 2=A little, 3=Moderately, 4=Quite a bit, 5= Extremely). Two summary scores are generated by summing individual items on the 'physical' and 'psychological' domains and then transforming the scores using a 1-100 scale. High scores indicate worse health and higher impact of MS.

Hobart et al., (2001) report on the psychometric properties of the MSIS-29 based on the results of a separate postal survey of 1250 MS society members. They report that the MSIS-29 satisfied all psychometric criteria: missing data was low (maximum 3.9 percent) and item test-retest reliability was high ($r=.65-.90$). MSIS-29 scales showed good variability, small floor and ceiling effects and high internal consistency (Cronbach's $\alpha \geq .91$). There was evidence for good

convergent validity. For example, the MSIS-29 physical scale correlated most with the Functional Analysis of MS physical scale ($r=.88$) and the psychological scale correlated most with the Short Form Health Survey mental health scale ($r=.76$). The MSIS-29 also confirmed group differences. For example, people who were retired due to MS scored significantly higher ($p<.001$) than those who were still employed. A further study in which the MSIS-29 was used in three hospital-based samples produced similar psychometric findings, supporting the use of the MSIS-29 in different clinical settings (Riazi et al., 2002). More recently, comparison of the MSIS-29 with other self-report scales revealed that the MSIS-29 was the most sensitive physical scale and second most sensitive psychological scale (behind the General Health Questionnaire-12 (Hobart et al., 2005). Hobart and colleagues (2004) provide classification for scores on the MSIS-29 in which scores of 0-19 are categorised as “no problems, scores of 20-39 as “few problems”, scores of 40-59 as “moderate problems”, 60-79 as “quite a few problems” and 80-100 as “extreme problems”.

Therefore, the current study will explore the performance of a group of people with MS on measures of executive function, ToM, empathy and quality of life.

Chapter 3 Results

3.1 Structure of Analysis

Initially, the descriptive characteristics of the MS sample were summarised. The analysis then focused on the performance of the MS sample on the tests of executive functioning (Mental Flexibility, Inhibition and Response to Feedback) and processing speed. Particular attention was paid to noting the proportion of the sample scoring one standard deviation (1SD) or more below the published normative mean. Using the criteria of 1SD or more below the normative mean as an indication of impaired performance is recommended by Taylor & Heaton (2001). Taylor and Heaton (2001) compared the sensitivity and specificity of using cut-off values of 1SD, 1.5SD and 2SD below the mean for classifying cases as 'normal' or 'abnormal'. They reported that using a cut-off of 1SD below the mean achieved the optimal balance between sensitivity and specificity. Using a cut-off of 1.5 or 2SD below the mean resulted in only modest gains in specificity and larger losses in sensitivity (i.e. increased risk of missing potential clinical cases). However, it is important to recognise that approximately 15.9% of the normal population would be expected to obtain scores greater than 1SD below test means (Lezak et al., 2004). With this caveat in mind, scores of 1SD or more below the normative have been considered to represent potentially impaired performance in the current study.

Performance on the ToM tests was then summarised and compared to published data from healthy participants. Scores on the empathy and quality of life questionnaires were also summarised and compared to published normative data. For hypothesis-driven results, analyses using Pearson's Product Moment

Correlations were completed. Additional exploratory analyses were then conducted.

3.2 Participants

208 invitation letters were sent to patients listed on the Department of Neurology (NHS Grampian) MS database. Initially 49 people agreed to take part in the study. However, four were unable to take part because they experienced a relapse and three people decided not to take part because of the distance or transport costs involved. Of the remaining 42 MS participants (20.2% response rate) who completed the assessment appointment 38 (18.3% response rate) returned completed questionnaires. Other-rater measures of empathy were returned by 32 people.

3.3 Initial exploratory analysis

The distribution of the test data was investigated by plotting histograms for each of the outcome variables. The reasonably symmetrical distributions suggested that the data were normally distributed. Furthermore, the values of skewness and kurtosis were non-significant suggesting normal distribution of data.

Potential outliers were identified using scatterplots and boxplots. This process highlighted two extreme cases in the Feedback outcome variable, two for the IRI self-report and one for IRI other-report. For the current data, individual z-scores for each of the outcome variables fell within what would be expected within a normal distribution. Consequently, outlier scores were retained for analysis.

3.4 Demographic Characteristics of sample

3.4.1 Age, estimated years of education and Estimated Premorbid IQ

The aim was to recruit a broad sample of people with a diagnosis of MS: including individuals experiencing a range of physical and psychological consequences of MS. Only individuals who were judged by their Consultant Neurologist to be incapable of taking part were excluded. Therefore, the sample consisted of 31 females (73.8%) and 11 (26.2%) males. The sample's mean age, estimated years of education and NART-estimated premorbid IQ score are shown in Table 3.1.

Table 3.1: Demographic Characteristics of sample and NART estimated IQ

	Mean	SD	Range (min-max)
Age	44.93	9.26	22 - 61
Estimated years of education	15.10	3.38	10-22
NART estimated FSIQ	111.24	7.17	94-124

3.4.2 MS Characteristics: Type of MS, years since diagnosis, reported physical disability

As figure 3.1 shows, the majority of the sample had a diagnosis of Relapsing Remitting MS (n= 30; 69.0%). Secondary Progressive MS was the next most frequent type (n = 9; 21.4%), followed by Primary Progressive MS (n = 3; 7.1%). One participant (2.4% of sample) reported not being aware of having a diagnosis of a specific MS sub-type.

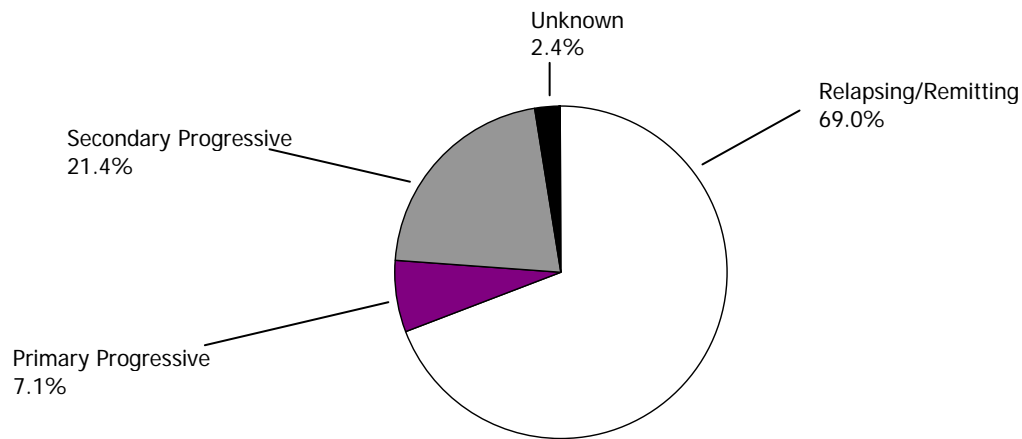


Figure 3.1: Proportion of MS sub-types within the MS sample

The data describing years since diagnosis and self-reported physical disability in the MS sample are shown in Table 3.2.

Table 3.2: MS Characteristics

	Mean	SD	Range(min-max)
Years since diagnosis	8.98	6.56	1-35
Physical Disability (self-report Disease Steps score)	2.27	1.78	0-6

Self-reported Disease Steps score was used as a measure of MS severity based on physical disability. Participants' scores ranged from ratings of 0 = "functionally normal with no limitations on activity or lifestyle" to 6 = "patients are essentially confined to a wheelchair or scooter".

3.4.3 Anxiety and Depression: Hospital Anxiety and Depression Scale subscale scores (HADS)

The sample's HADS subscale scores for symptoms of anxiety and depression are shown in Table 3.3.

Table 3.3: Self-Report HADS scores.

	Mean	SD	Range (min-max)
HADS – Anxiety	8.17	4.76	1-21
HADS – Depression	5.14	4.08	0-20

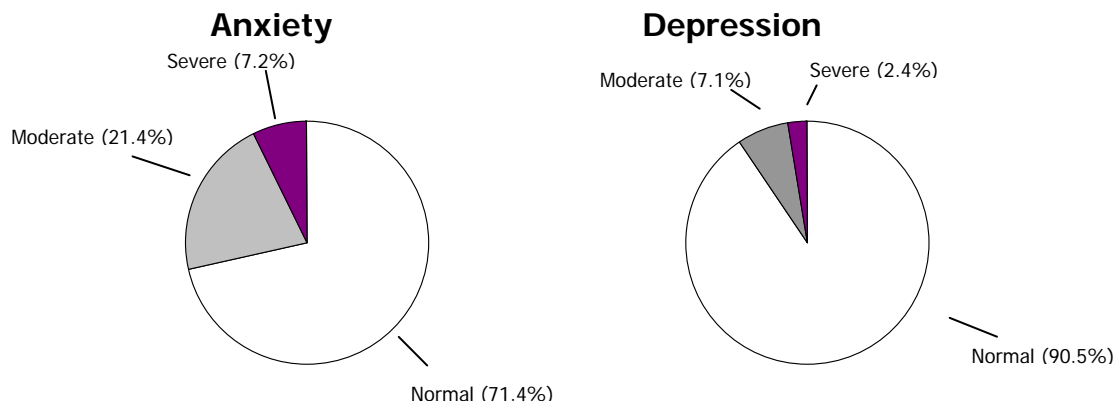


Figure 3.2: Rates of clinical cases of anxiety or depression based on self-report HADS scores using the cut-off scores recommended by Crawford et al., (2001).

Using the cut-off scores recommended by Crawford et al., (2001), 28.6% (12) of participants scored within the clinical range for anxiety symptoms and 9.5% (4) participants scored within the clinical range for symptoms of depression (Figure 3.2).

3.5 Tests of Executive Functioning

3.5.1 Descriptive Information for the Verbal Fluency Test

Normative data for the Verbal Fluency Test (Gladsjo et al., 1999) utilises T-scores (Mean = 50, SD = 10). In doing so, raw scores are adjusted to take account of a participant's age and estimated years of education. Table 3.4 shows the mean T-score for letter fluency (combined F, A, S) was 40.98, with scores ranging from 26 to 60. Overall, 50% (n = 21) of the MS sample scored at or below a T-score of 40, which is equivalent to 1SD below the normative mean. None of the MS participants scored above a T score of 60, which is equivalent to 1SD above the normative Mean.

For Category Fluency (category of 'animals'), the mean T-score was 42.19 (range 21 to 74), with 45.2% (n = 16) scoring below a T-score of 40 (equivalent to 1SD below the mean).

Table 3.4: Means, standard deviations (SD) and minimum and maximum values for raw test scores and converted T-scores on the letter and category part of the Verbal Fluency test.

Test Score	Mean	SD	Range (Min-Max)
Letter Fluency Raw Score (F,A,S)	34.33	8.74	17 – 56
Letter Fluency T score	40.98	8.45	26 - 60
Category Fluency Raw Score (animals)	18.95	5.20	10 – 33
Category Fluency T score	42.19	11.22	21 - 74

3.5.2 Descriptive Information for the Hayling Test

Table 3.5 highlights that, as expected, participants responded faster in Hayling Test 1 (which measures initiation and response speed) than Hayling Test 2 (which measures response inhibition).

Table 3.5 Means, standard deviations (SD) and ranges for Hayling Test scores

Test	Mean	SD	Range (Min-Max)
Hayling Test Time 1 (seconds)	7.98	7.35	0 – 29
Hayling Test Time 2 (seconds)	48.29	30.11	2 – 116
Hayling Total Response Error Score	5.12	2.39	1 - 8
Hayling Total Scaled Score	15.83	3.26	9 – 20

Based upon the normative data published in the test manual (Burgess & Shallice, 1997), analysis of participants' scaled scores revealed that overall, the sample performed within the average range on the Hayling Test: with a mean total Hayling scaled score of 15.83 (SD = 3.26). To explore the proportion of participant's scoring below average on the Hayling Test, participant's scaled scores were analysed at the individual level. Overall, nine participants (21.4%) scored 1SD or more below the normative mean on the Hayling Test. For further details on performance on the Hayling Test, including error analysis, see Appendix 18.

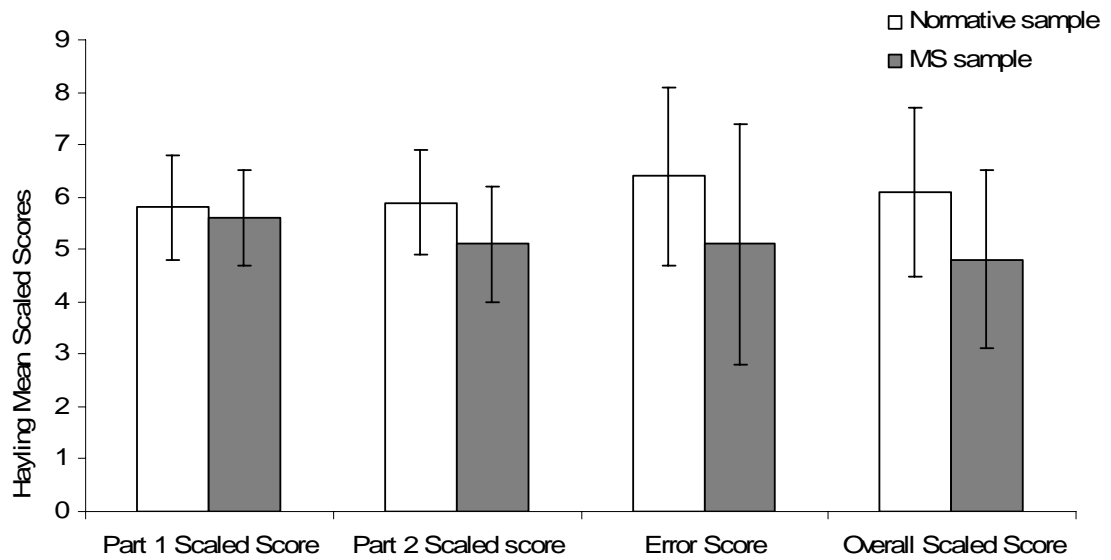


Figure 3.3 Comparison between the mean Hayling scaled scores (error bars show Standard Deviation) from the current MS sample (grey) and published normative data (white), Burgess & Shallice (1997).

Figure 3.3 shows that the sample which formed the published normative data (n=71; Burgess & Shallice, 1997) scored higher on all aspects of the Hayling Test than the current MS sample.

3.5.3 Descriptive Information for the Brixton Test

Using Burgess and Shallice's (1997) normative data, Table 3.6 illustrates that the mean number of errors made by MS participants on the Brixton Test classified group performance within the average range (Error Score 14-17). The MS sample's Brixton scaled score was also within the average range.

Table 3.6 Mean, standard deviation (SD) and range for Brixton Test

Test	Mean	SD	Range (Min-Max)
Brixton Error Score	16.38	6.72	7 - 33
Brixton Scaled Score	5.79	1.98	1 – 9

In order to explore the proportion of participants scoring below average on the Brixton Test, scaled scores were analysed at the individual level. The majority of participants scored within the 'average' (19.0%) to 'high average' (33.3%) range (see Appendix 19). Six participants (14.3%) were classified as above average, whilst a further six (14.8%) scored within the 'impaired' to 'poor' range of functioning. Overall, ten participants (23.8%) scored 1SD or more below the normative mean.

3.5.4 Descriptive Information for the Colour Trails Test

Table 3.7 summarises performance on CTT1, a measure of visual scanning and information processing speed. Overall, 33.3% of the MS sample scored 1SD or more below the normative mean.

Table 3.7 Mean, standard deviation (SD) and range for Colour Trails 1 (CTT 1)

Test	Mean	SD	Range (Min-Max)
Colour Trails Test 1 (seconds)	44.57	19.36	18 – 120

3.5.5 Summary of Neuropsychological Assessments

Taking a score of 1SD or more below the mean as evidence of potential impairment, Figure 3.4 shows the percentage of cases in the current MS sample that scored within the potentially impaired range on the neuropsychological assessments. The largest proportion of MS participants scoring 1SD or more below the mean was on the Letter Fluency test.

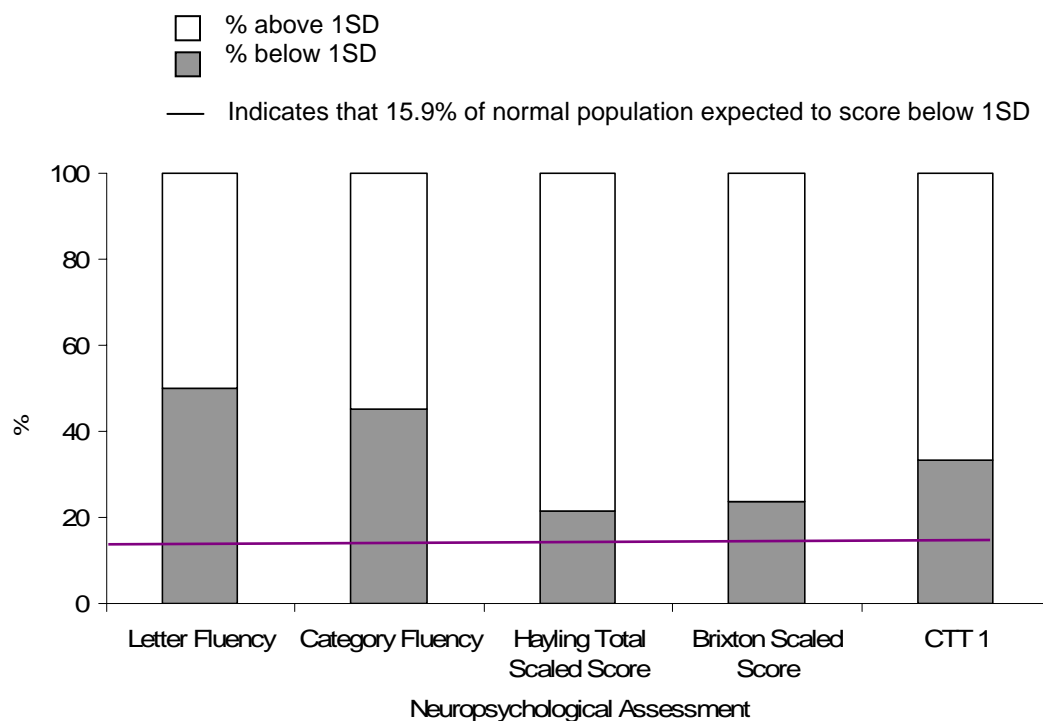


Figure 3.4 Bar graph showing the percentage of cases scoring at or below 1SD below the normative mean on the neuropsychological assessments completed in this study.

3.6 Tests of Theory of Mind

One participant was not able to complete the ToM Stories Test because of fatigue. Therefore, only 41 participants completed the Stories Test.

Table 3.8 Means, standard deviations (SD) and ranges for test scores on the Eyes Test, Videos Test, Stories Test and control versions of these tests.

Test	Mean % Correct	SD	Range (Min – Max)
ToM Eyes	69.6	14.8	34.6-92.3
Control Eyes	51.5	13.8	24.0-92.0
ToM Videos	60.1	11.9	37.5-81.3
Control Videos	66.7	14.1	37.5-87.5
ToM Stories	72.4	16.2	33.3-100.0
Control Stories	79.7	14.7	33.3-100.0

Table 3.8 illustrates that, for the ToM tests, the MS sample achieved their highest mean score on the Stories Test, followed by the Eyes Test, then the Videos Test. Across all three ToM measures, there was a very broad range of scores. Performance on the Stories and Videos control versions of the tests was superior compared to the ToM versions, whereas for the Eyes Test participants' showed superior performance on the ToM version of the task compared to the control version of the task. As the Videos and Stories ToM tests are still being developed, normative data similar to that reported for the established neuropsychological assessments was not available to classify the performance of the MS sample.

3.7 Empathy

3.7.1 Empathy Quotient

Table 3.9 summarises Self and Other-report data for the EQ. Self and Other report mean scores were very similar. Indeed, there was a significant correlation between the self and other-rater responses on the EQ ($r = .67$, $p < .001$) and a t-test confirmed that there was no significant difference between the self and other mean scores ($t(31) = -.021$, $p = .983$).

Table 3.9: Descriptive Information for the Self and Other-Report data for the Empathy Quotient.

Empathy Quotient Questionnaire	Mean	SD	Range (Min-Max)
Self-Report	44.90	11.95	23 – 66
Other-Report	45.52	15.08	16 – 69

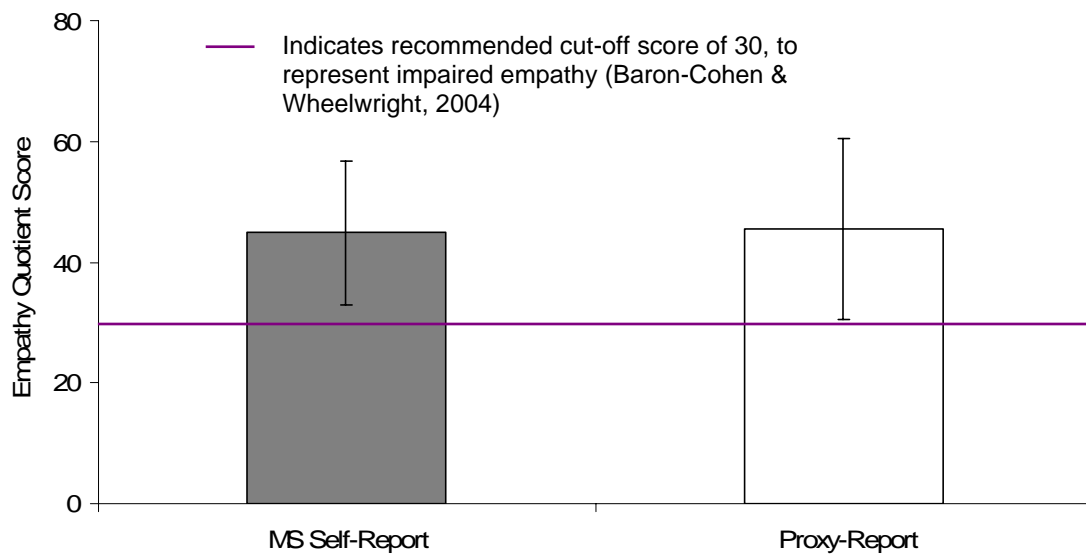


Figure 3.5: Mean EQ self-report and other-report scores. Error bars show standard deviation.

Mean self-report and other-report empathy scores were very similar (Figure 3.5). In the MS group, only five individuals (13.2%) scored below the level proposed to indicate evidence of impaired empathic abilities. Consistent with this result, other-ratings also classified five individuals (16.1%) as demonstrating potentially impaired empathy.

3.7.2 Interpersonal Reactivity Index

Figure 3.6 compares the mean self and other-report data for the four IRI subscales. There were significant, positive correlations between the self and other ratings on each subscale ($n = 32$, $p < .05$). T-tests confirmed that there were no significant differences between the self and other mean IRI scores (all ns).

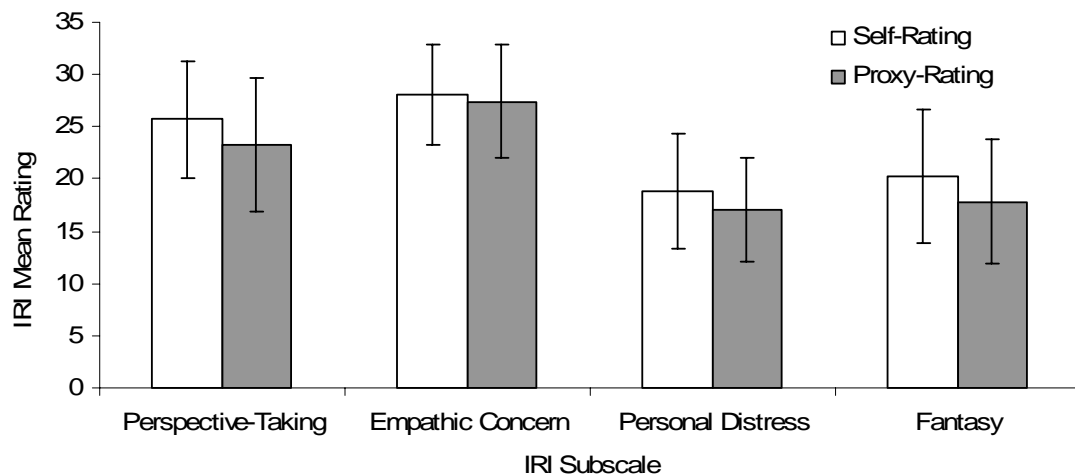


Figure 3.6: Self and other mean scores for the four subscales of the Interpersonal Reactivity Index. Error bars show standard deviation.

3.8 Quality of Life Self-Report

3.8.1 WHO QoL-BREF

Figure 3.7 shows the mean scores for the MS sample and for population norms (Hawthorne et al., 2006) for the WHO QoL-BREF domains of Physical, Psychological, Social and Environment-related quality of life. The MS sample reported their highest QoL in the Environment domain, followed by the Social Relationships domain. The MS sample reported similar low mean QoL scores in the Psychological and Physical domains.

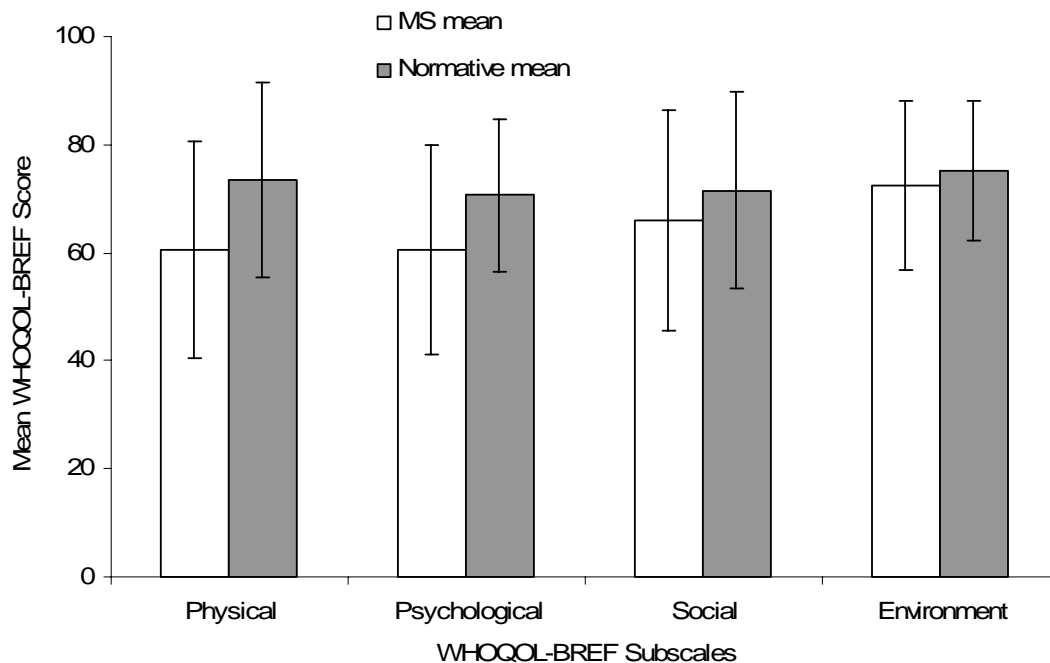


Figure 3.7: Bar graph showing mean WHOQOL-BREF scores for the MS sample (white) and a healthy, community-based population (n=866) (grey) published by Hawthorne et al., (2006). Error bars show standard deviation.

3.8.2 Multiple Sclerosis Impact Scale

The level of self-report physical impact (Mean = 33.06, SD = 27.96) and psychological impact of MS (Mean = 35.28, SD = 22.31) were very similar (Figure 3.8). According to Hobart et al. (2004), these mean scores would classify the current sample as experiencing “few problems” according to the MSIS-29 physical and psychological subscale scores.

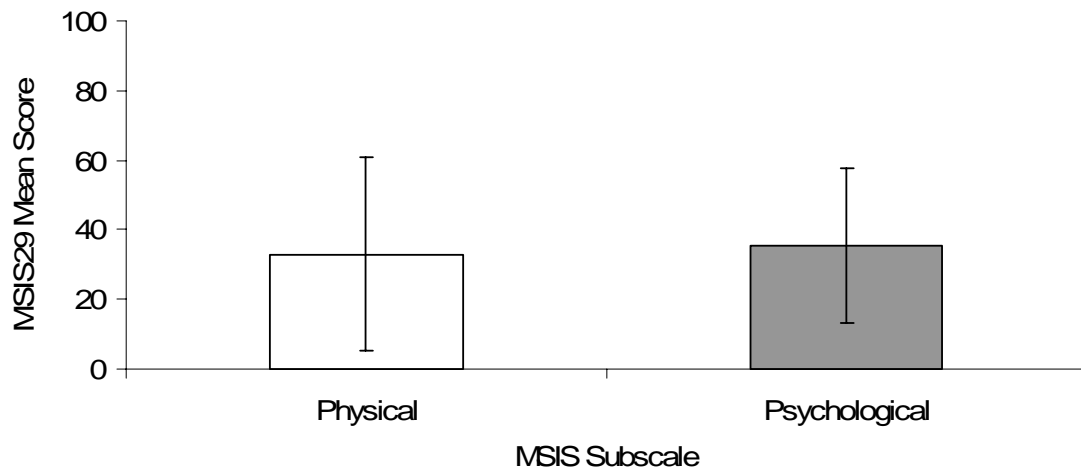


Figure 3.8 Mean MSIS-29 scores for the Physical and Psychological Domains. Error bars show standard deviation.

3.9 Hypothesis Driven Results

One of the study's main aims was to investigate the relationships between social cognition measures (ToM and empathy) and performance on neuropsychological measures of executive functioning - particularly tapping Mental Flexibility, Inhibition and Response to Feedback. Pearson product-moment correlation coefficients were used to measure the strength of statistical association between ToM performance, empathy ratings, performance on neuropsychological tests of executive functioning and QoL measures. For all correlational analyses, scatterplots were first inspected (see appendix 19).

3.9.1 Hypothesis 1: Reduced performance on measures of executive functioning (EF - Mental Flexibility, Inhibition and Response to Feedback) will be associated with reduced performance on Theory of Mind (ToM) tests.

It was predicted that significant, positive correlations between performance on tests of mental flexibility, inhibition and response to feedback and the ToM tests would be found. Also, that there would be a larger positive correlation between the executive functioning tests and ToM tests than between a measure of processing speed (CTT 1) and the EF tests. Bivariate, one-tailed correlations were calculated.

In support of hypothesis 1, there was a significant positive correlation between the composite EF (Mental Flexibility, Inhibition, Response to Feedback) and ToM measures (Eyes, Videos, Stories) $r=.55$ ($p<.001$). There was no significant relationship between composite EF performance and processing speed $r=.166$ ($p=.147$). A significance test for non-independent correlations (Williams, 1959)

revealed that the correlation between composite EF and ToM performance was significantly different to the correlation between EF and processing speed ($t = 2.09$, $df = 39$, $p = .02$).

A summary of the results of the correlational analyses for the individual EF and ToM tests is presented in Table 3.10. Using a Bonferroni correction, the adjusted p-value for an overall significance level of $p=.05$ was $p<.004$.

Table 3.10 Correlational analysis between Measures of Executive Function and Theory of Mind (n=42; except for Stories Test n=41)

	Mental Flexibility	Inhibition	Response to Feedback	Processing Speed
Eyes	.425*	.290	.365	.226
Videos	.025	.216	.243	.017
Stories	.329	.164	.515*	.228

* Correlation is significant at the .05 level (1-tailed)

In support of hypothesis 1, there was a significant positive correlation between participants' performance on the Eyes Test and Mental Flexibility $r=.425$ ($p=.003$). There was also a significant positive correlation between Feedback performance and the Stories Test $r = .515$ ($p<.001$). Correlations between performance on the Eyes Test and Response to Feedback $r=.365$ ($p=.009$) and Inhibition $r= .290$ ($p=.031$) and between performance on the Stories Test and Mental Flexibility $r = .329$ ($p=.018$) were not significant after correcting for

multiple comparisons. There were no significant correlations between EF performance and Videos ToM performance. As predicted, there were also no significant correlations between processing speed and ToM performance. Despite the pattern of significant correlations supporting hypothesis 1, William's Test revealed that there were no significant differences between the correlations in this analysis.

To examine whether the relationships between aspects of ToM performance and EF observed in this sample could be accounted for by MS severity, partial correlations in which Disease Steps score was held constant were calculated. The results (Table 3.11) showed that a positive relationship between performance on the Eyes Test and Mental Flexibility remained $r=.483$ ($p=.002$). A positive relationship between performance on the Stories Test and Response to Feedback $r=.505$, $p<.001$ also remained. Significance tests revealed that there were no significant differences between the partial and simple correlations for these two relationships, indicating that MS severity did not make a significant contribution to the relationships.

Table 3.11 Partial correlations between Executive Function and Theory of Mind Measures after controlling for physical MS severity (score on Disease Steps)

	Mental Flexibility	Inhibition	Response to Feedback
Eyes	.483*	.259	.282
Videos	.023	.197	.193
Stories	.353	.147	.505*

* Correlation is significant at the .05 level (1-tailed)

When partial correlations were conducted to control for participant age, the same two positive relationships emerged (Mental Flexibility and Eyes performance $r=.51$, $p=.001$ and Response to Feedback and Stories $r=.433$, $p=.005$). When NART-predicted IQ was controlled for, the significant, positive relationship between Response to Feedback and Stories remained ($r=.512$, $p=.001$) although the relationship between Mental Flexibility and Eyes was somewhat reduced ($r=.305$, $p=.05$).

Overall, there was very reasonable support for the hypothesis that there would be a positive relationship between EF and ToM performance, which would exceed the relationship between EF performance and processing speed in this MS sample. The positive relationships between Mental Flexibility and Eyes Test performance and association between Response to Feedback and Stories Test performance could not be accounted for on the basis of MS severity. These relationships also could not be accounted for on the basis of participant age or premorbid IQ.

3.9.2 Hypothesis 2: Reduced performance on measures of executive functioning (EF - Mental Flexibility, Inhibition and Response to Feedback) will be associated with reduced empathy.

It was further predicted that positive correlations between the EF measures and both the IRI perspective-taking subscale and the EQ would be stronger than the correlations between the EF measures and other IRI scales. Bivariate, one-tailed correlations were calculated (Table 3.12).

Table 3.12 Correlational analysis between Executive Functioning tests and EQ and Empathy measures

	Empathy Measures		Other IRI subscales		
	EQ Self-Report (n=38)	IRI Perspective-Taking (n=38)	IRI Empathic Concern (n=38)	IRI Personal Distress (n=38)	IRI Fantasy (n=38)
Mental Flexibility	.299*	.028	.170	-.077	.066
Inhibition	.101	.025	-.059	-.039	-.003
Response to Feedback	.003	.037	-.015	.025	.110

* Correlation is significant at the .05 level (1-tailed)

The only significant correlation was between performance on Mental Flexibility and the self-report EQ score ($r=.299$, $p=.034$, $n=38$). Testing for contrasts among non-independent correlations did not reveal a significant difference between the two groups of correlations. There were no other significant correlations between the empathy or other IRI subscales and the EF measures. Overall, there was very little association between the EF measures and the measures of empathy and thus hypothesis 2 was not supported.

3.9.3 Hypothesis 3: Reduced performance on measures of executive functioning (Mental Flexibility, Inhibition and Response to Feedback) will be associated with lower self-reported quality of life (QoL).

It was predicted that performance on EF tests would be positively associated with self-report QoL ratings. Specifically, it was predicted that there would be a stronger correlation between performance on EF tests and the Psychological and Social subscales of the WHOQOL-BREF compared to the Physical and Environment subscales. It was also predicted that there would be a stronger association between EF performance and the Psychological subscale of the MSIS-29 compared to the Physical subscale.

When correlational analyses were carried out (Table 3.13, the only significant correlation was between Inhibition performance and self-reported QoL in the Environmental domain $r = .288$, $p = .040$ ($n = 38$).

Table 3.13 Correlational analysis between Measures of Executive Functioning and Quality of life

	WHO QoL-BREF				MSIS	
	Physical Score (n=38)	Psych Score (n=38)	Social Score (n=38)	Enviro. Score (n=38)	MSIS Physical (n=40)	MSIS Psych (n=40)
Mental Flexibility	-.019	.182	.028	.162	.040	-.258
Inhibition	.185	.139	.181	.288*	-.183	-.144
Response to Feedback	.105	-.141	.011	-.101	-.217	-.084

* Correlation is significant at the .05 level (1-tailed)

Correlations between performance on Mental Flexibility and the MSIS-29 Psychological subscale $r=-.258$, $p=.054$ ($n=40$) and performance on Response to Feedback and the MSIS Physical subscale $r=-.258$, $p=.054$ ($n=40$) did not reach significance. The correlations were negative because the MSIS-29 measures the impact of MS so a higher score indicates greater impact of MS. There were no other significant correlations or clear patterns in the data.

After adjusting the significance level to account for multiple comparisons (adjusted significance level $p=.002$) none of the correlations between EF performance and QoL remained significant. Consequently, the hypothesis that EF performance would be associated with self-reported QoL in this MS sample was not supported.

3.9.4 Hypothesis 4: Reduced performance on measures of ToM ability (Eyes, Videos and Stories Tests) will be associated with lower self-reported quality of life.

It was predicted that performance on ToM measures would be positively associated with self-report QoL ratings. Specifically, it was predicted that there would be a stronger correlation between performance on ToM tests and the Psychological and Social subscales of the WHOQOL-BREF compared to the Physical and Environment subscales. It was also predicted that there would be a stronger association between ToM performance and the Psychological subscale of the MSIS-29 compared to the physical subscale.

There were no significant correlations between ToM performance and QoL (Table 3.14). Consequently, the hypothesis that ToM performance would be associated with self-reported QoL in this MS sample was not supported.

Table 3.14 Correlational analysis between Measures of ToM Ability and Quality of life

	WHO QoL-BREF				MSIS	
	Physical Score (n=38)	Psych Score (n=38)	Social Score (n=38)	Enviro. Score (n=38)	MSIS Physical (n=40)	MSIS Psych (n=40)
Eyes	.117	.125	.171	.240	-.153	-.196
Videos	-.229	-.110	-.069	-.110	.008	.110
Stories	.042	-.145	.002	.113	-.059	-.037

3.10 Additional Research Questions

3.10.1 Does MS affect ToM and Empathy differently?

Overall, the results indicated that there was some evidence to suggest that ToM performance was impaired according to performance on the Eyes Test in this MS sample. In contrast, there was no consistent evidence for reduced empathy in the current sample.

Correlational analyses between ToM performance (Eyes, Videos and Stories Tests) and Empathy measures (EQ and IRI) revealed a weak correlation between Eyes Test performance and the EQ ($r = .35$, $p = .025$) as well as the Perspective-

Taking subscale of the IRI ($r = .30$, $p = .036$). There were no other significant correlations. These results indicate that in this sample, aspects of ToM performance were impaired whereas affective empathy appeared intact. Furthermore, correlational analyses indicated that there were no significant associations between ToM performance and measures of affective empathy. However, there were weak associations between ToM performance on the Eyes Test and the two cognitive empathy scales (thought to tap ToM), the EQ and Perspective-Taking subscale of the IRI.

3.10.2 Do empathy measures in MS vary according to information source?

As discussed in Section 3.7.1, there were no significant differences between the mean self and other-rater empathy ratings, demonstrating that in this MS sample empathy ratings did not vary significantly according to information source.

3.11 Results summary

In the current MS sample, the results provided evidence to support Hypothesis 1, that reduced executive functioning performance was associated with reduced ToM performance. More specifically, reduced performance on Mental Flexibility and Response to Feedback tests was associated with poorer performance on the Eyes and Stories ToM Tests. There was very limited support for Hypothesis 2 (that reduced executive functioning performance was associated with lower empathy) as the only significant association was between mental flexibility and EQ score. No consistent evidence to support Hypotheses 3 was found in the current sample. However, the QoL scores highlighted that participants experienced the physical and psychological effects of MS as having a similar impact.

In terms of clinical relevance, using a score of 1SD or more below the normative mean as a cut-off point for clinically-relevant impairment, 50% of the MS sample scored within the potentially impaired range on the letter fluency test, 42.5% on the category fluency test, 33.3% on the Colour Trails 1, 23.8% on the Brixton and 21.4% on the Hayling Test.

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Chapter 4 Discussion

MS is the most common disabling neurological condition among young adults, affecting approximately 85,000 people in the UK (Neild, 2006). The impact of MS on physical abilities has long been known, and recognition of the potential impact of MS on various aspects of cognition, mood and quality of life is now increasing. The potential psychological consequences of MS are now included in the MS National Institute of Clinical Excellence guidelines (NICE, 2003). The relevance of investigations of the impact of MS on aspects of social cognition is highlighted by recent evidence that white matter pathology has a particular effect on social cognition (Charlton et al., 2009; Green et al., 2004). The present study aimed to investigate the relationship between performance on measures of specific executive functioning abilities (mental flexibility, inhibition and response to feedback) and two types of social cognition (ToM performance and empathy) in an MS sample. An additional aim was to explore whether performance on executive functioning tests, ToM tests and empathy measures had a stronger association with Psychological and Social quality of life than with Physical quality of life. The inclusion of other-report data on the empathy measures also provided information relating to insight and reliability of self-report in MS.

4.1 General Findings

4.1.1 Demographic Characteristics of the sample

Overall, the demographic characteristics of the current sample suggested that they were reasonably well-educated, as reflected in their estimated premorbid IQ. The demographic characteristics were well-matched to those reported by Henry et al., (2009) in their sample of 27 MS participants: mean age of 47.0 years (range 26-64 years) and mean years of education of 15.0 years.

4.1.2 MS Characteristics of the sample

In this sample, the proportion of participants with Relapsing/Remitting MS (69%), Secondary Progressive MS (21%) and Primary Progressive MS (7%) was broadly consistent with the rates reported for the UK population (Compston & Coles, 2008). This sample was also representative of gender distribution, in that it comprised 31 females (74%) and 11 males (26%). Average age at diagnosis (35.9 years) was consistent with previous reports (Compston & Coles, 2008). Average time since diagnosis (8.9 years) was shorter than time since symptom onset (13.8 years), which may reflect a degree of delay in diagnosis, as reported by Edwards et al., (2008).

In terms of physical MS severity and disability, the mean self-reported Disease Steps score was 2.3 (SD=1.78), encompassing the full range of scores (from 0=normal to 6=confined to wheelchair). The Disease Steps correlates strongly ($r=.96$) with the neurologist-scored disability rating scale, the Kurzke Expanded Disability Status Scale (Hohol et al., 1999). The Disease Steps score was likely influenced by the high proportion of the sample with Relapsing/Remitting MS,

as people with this form of MS have been reported to accumulate physical disability more slowly than those with progressive forms of the disease (Confavreux et al., 2000). The level of physical MS severity was equivalent to that reported (Mean = 1.9, SD=1.98) in the study by Henry et al., (2009).

4.1.3 Depression

A low rate of depression was observed. Only four participants (9.5%) scored within the clinically significant range for symptoms of depression on the HADS, based on the cut-off score of 11, recommended by Crawford et al., (2001). Using Zigmond and Snaith's (1983) classifications for moderate and severe clinical cases on the HADS, three participants (7.1%) and one participant (2.4%) scored in the moderate and severe ranges respectively. This rate of depression was low compared to the reported lifetime prevalence of depression in MS of 50% (Minden & Schiffer, 1990). The current level of depression was also lower than that reported in a recent study (31.4% - Bieske et al., 2008). However, other recent studies reported lower rates of depression in their samples (Drew et al., 2008; Henry et al., 2009). For instance, Summers and colleagues (2008) also used the HADS and reported an almost identical rate of depression to the current sample (9%, 4 out of 45 participants). It is clear that research findings concerning depression in MS can be conflicting (Dalton & Heinrichs, 2005).

The issue of depression prevalence in MS is complex. Reported findings should be considered in the context of the following potential influences:

- (1) The use of inappropriate measures of depression, such as those including items sensitive to MS symptoms, (for example, fatigue and

psychomotor symptoms). In the current study as well as those of Drew et al., (2008) and Henry et al., (2009), measures of depression were selected to minimise the likelihood of MS symptoms influencing depression scores.

(2) The use of different measures across different samples also makes meaningful comparison of results problematic.

(3) Recruitment methods should also be considered, as those people with depression may be less likely to participate in some studies.

This issue will be discussed in more detail in section 4.6.1.

4.1.4 Anxiety

A moderate rate of anxiety was found, with 12 participants (28.6%) reporting anxiety symptoms within the clinical range on the HADS. Of those scoring within the clinically significant range, nine participants (21.4%) scored within the moderate range and 3 (7.2%) in the severe range. Previous research findings vary widely: reporting the prevalence of anxiety in MS between 19 and 90 percent (Feinstein et al., 1999; Korostil & Feinstein, 2007; Minden & Schiffer, 1991; Noy et al., 1995; Pepper et al., 1993; Stenager et al., 1994). Once again, the rates of anxiety as measured by the HADS in this sample were almost identical to those recently reported by Summers and colleagues (12 out of 45 participants, 27%).

Anxiety in MS has been characterised as a reactive psychological response (Zorzon et al., 2001). Reported evidence of a stronger link between anxiety and experience of relapse (McCabe, 2005) appears to support this account. In the

current study, examination of HADS anxiety scores for participants with Relapsing Remitting MS compared to those with Secondary Progressive MS did not suggest evidence for increased anxiety in the Relapsing Remitting group. As with depression, the variability in reported levels of anxiety between studies is likely to be due in part to variation in the selection of anxiety measures.

4.1.5 Executive functioning performance

In terms of overall performance on the executive functioning tests, 50% of the MS sample scored within the potentially clinically impaired range (1SD or more below the normative mean) on a measure of Mental Flexibility, 38.1% for Inhibition, and 23.8% for Response to Feedback. As only around 16% of the normal population would be expected to score 1SD or more from the mean on these assessments, these percentages indicate likely clinical impairment amongst some MS participants.

Eighty-one percent of the MS sample scored within the impaired range on at least one test of executive functioning. This evidence for widespread impairment of aspects of executive functioning in MS was consistent with the recent findings of Drew et al., (2008). They reported that 66% of their MS sample (n=95) scored 1SD or more below the standardised mean on at least one executive function measure (D-KEFS, Delis et al., 2001). Taken together, these findings indicate that rates of executive functioning impairment in MS may be considerably higher than previous reports of 15-20% (e.g. Rao et al., 1991). Higher rates of executive impairment may, in part, reflect the more

comprehensive and specialist assessment of executive function in the current study and that carried out by Drew and colleagues (2008).

Comparison between performances on the three executive function measures revealed that Mental Flexibility performance (as measured by letter fluency) was most impaired in this sample. This finding is consistent with evidence from meta-analyses suggesting that verbal fluency is amongst the most sensitive neuropsychological measure to cognitive impairment in MS (see Henry & Beatty, 2006). It is possible that anxiety may have played a role in this finding. Anxiety is known to impact negatively on letter fluency performance (e.g. Lezak et al., 2004) and a relatively high level of anxiety was reported in this sample. Furthermore, there was a significant relationship between HADS anxiety score and Mental Flexibility performance ($r = -.34$). There was no relationship between anxiety and the other two EF measures.

Ten participants (23.8%) demonstrated impaired problem-solving in Response to Feedback (as measured by the Brixton Spatial Anticipation Test). Similarly, nine participants (21.4%) scored within the potentially impaired range for Inhibition (as measured by the Hayling Sentence Completion Test). These results were generally consistent with previous evidence of the impact of MS on executive functions such as shifting, inhibition and fluency (Beatty et al., 1989; Beatty & Monson, 1996; Summers et al., 2008).

Performance on a measure of Processing Speed (Colour Trails I) was important to include in the assessment battery because reduced processing speed is

viewed as a fundamental aspect of MS-related cognitive impairment (Kujala et al., 1994). Furthermore, the potential for reduced processing speed to negatively impact many other aspects of cognition makes inclusion of a processing speed measure an important part of any cognitive assessment for MS. According to the criteria used in the current study, 14 participants (33%) demonstrated potentially impaired processing speed.

4.1.6 ToM performance

Due to the lack of normative data, unfortunately it was not possible to compare the performance of the current MS sample with a matched-control group from previously published data on the Videos and Stories Tests, so comparisons focused on the Eyes Test.

Figure 4.1 compares performance on the Eyes Test by the current MS sample with previously published data. The mean percent correct score on the Eyes Test for the current MS sample (69%) was very similar to that obtained by the MS sample in Henry et al's (2009) study (70%). Data for the control participants in Henry et al's (2009) study (79% correct) and in Baron-Cohen et al's (2001) study (77%) are shown for comparison. The current results appear to replicate Henry et al's (2009) finding. In the study carried out by Henry et al., (2009), performance of the MS participants (n=30) on this ToM test was significantly impaired compared to the healthy participants.

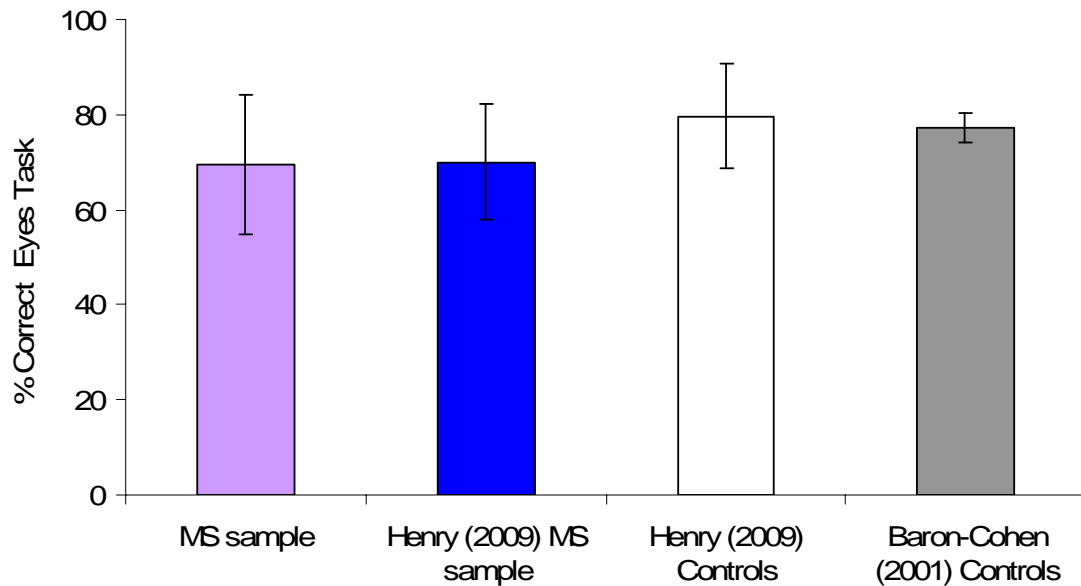


Figure 4.1 Mean % correct scores for the Eyes Test in the current MS sample ($n = 42$) compared to the MS and control samples ($n=30$, $n=239$) reported by Henry et al., (2009) and by Baron-Cohen et al., (2001) respectively. Error bars show Standard Deviation.

Comparison of Eyes performance between the current MS group with the MS group and healthy control data provided by Henry et al., (2009) suggests further evidence that MS is associated with impaired ToM abilities (as measured by this test).

4.1.7 Empathy

No significant differences between self and other-report data on the two empathy measures used in the current study (EQ and IRI) were demonstrated. These findings suggest that the current MS group demonstrated intact awareness regarding their empathy abilities. This issue will be discussed in more detail in Section 4.3.1.

Figure 4.2 compares the mean self and other-report data on the EQ with that reported by Baron-Cohen and Wheelwright (2004) in a group of healthy participants and individuals with High-Functioning Autism or Asperger's Syndrome. The mean score of the current MS group on the EQ was equivalent to the mean score reported by Baron-Cohen and Wheelwright (2004) for their control group. Inclusion of the mean score on the EQ obtained by a group of individuals with High-Functioning Autism or Asperger's Syndrome highlights the extent of empathy impairment observed on the EQ in a different patient group (Baron-Cohen & Wheelwright, 2004). These results indicate that the current MS group did not demonstrate evidence of impaired empathy compared to other-ratings or data from healthy participants on the EQ.

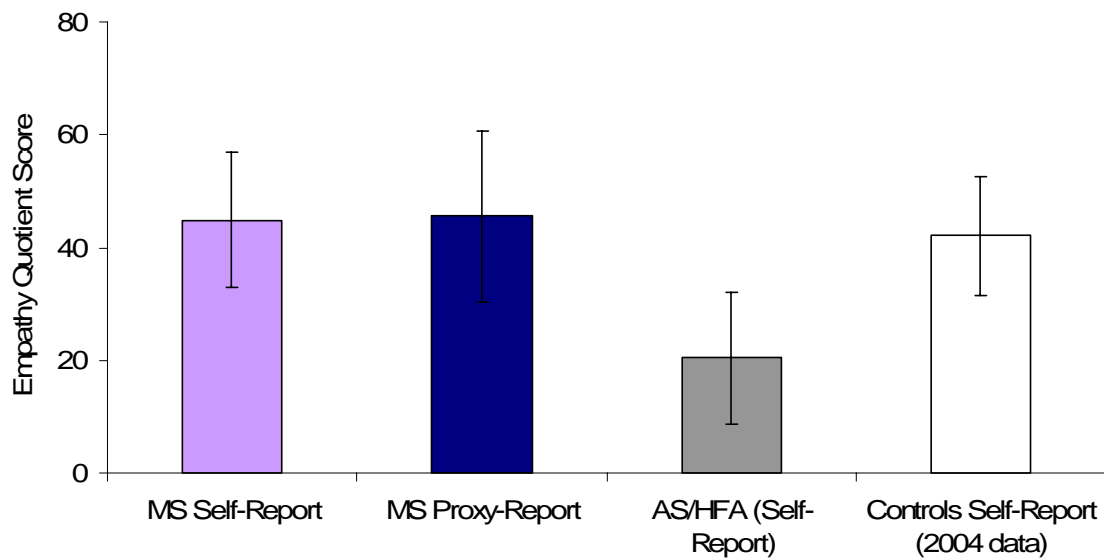


Figure 4.2 Bar graph showing mean EQ scores from the current MS sample, a group of individuals with high-functioning autism or Asperger's syndrome ($n = 90$, AS/HFA) and a control sample ($n = 90$, data from Baron-Cohen & Wheelwright, 2004). Error bars show standard deviation.

The evidence for intact empathy in this MS sample stands in contrast to the only other study which has directly measured empathy abilities in MS, to the author's knowledge. As discussed previously, Benedict et al., (2001) reported significant differences between self and other reports on the Hogan Empathy Scale in their MS sample, with MS participants generating higher self-ratings compared to other-ratings. One limitation of Benedict et al.'s study was their recruitment of individuals with MS who were experiencing "emotional problems". The evidence for preserved empathic abilities in the current MS sample is strengthened by the comparable self and other-reports demonstrated on two separate measures of empathy (EQ and IRI).

4.1.8 Quality of Life (QoL) in MS

The current MS sample reported reduced QoL across all four domains covered by the WHO QoL-BREF (Physical, Psychological, Social and Environment) in comparison to the normative data reported by Hawthorne et al., (2006). This is in agreement with consistent evidence suggesting reduced QoL in MS compared to healthy participants (e.g. Wynia et al., 2008). Although interpretation in this study is limited because of the reliance on previously published control data, it is interesting to note that the current MS group reported equivalent Physical and Psychological QoL, rather than the more frequent pattern of lower Physical QoL compared to other domains (e.g. Benedict et al., 2005). Comparison of the current data with recently reported data from another MS sample on the WHO QoL-BREF (Phillips et al., 2008) highlighted similar scores for the domains of Psychological, Social and Environmental QoL. However, the current MS sample reported higher Physical QoL. As well as the potential influence of the inherent

variability found in MS, other relevant factors relating to this discrepancy could include differences in the type and severity of MS experienced by participants. Similar ratios of Relapsing Remitting and Progressive MS cases were included in both studies. Unfortunately, Phillips et al., (2008) did not report a measure of disease severity, although they did report average disease duration of 11.8 years in their sample. It is not clear whether this figure relates to duration since diagnosis or symptom onset. In the current MS sample, disease duration since symptom onset was 13.95 years and duration since diagnosis was 9.0 years. Recruitment method may also have influenced the physical severity score of MS participants in both studies as participants in the Phillips et al., (2008) study were visited at home if required.

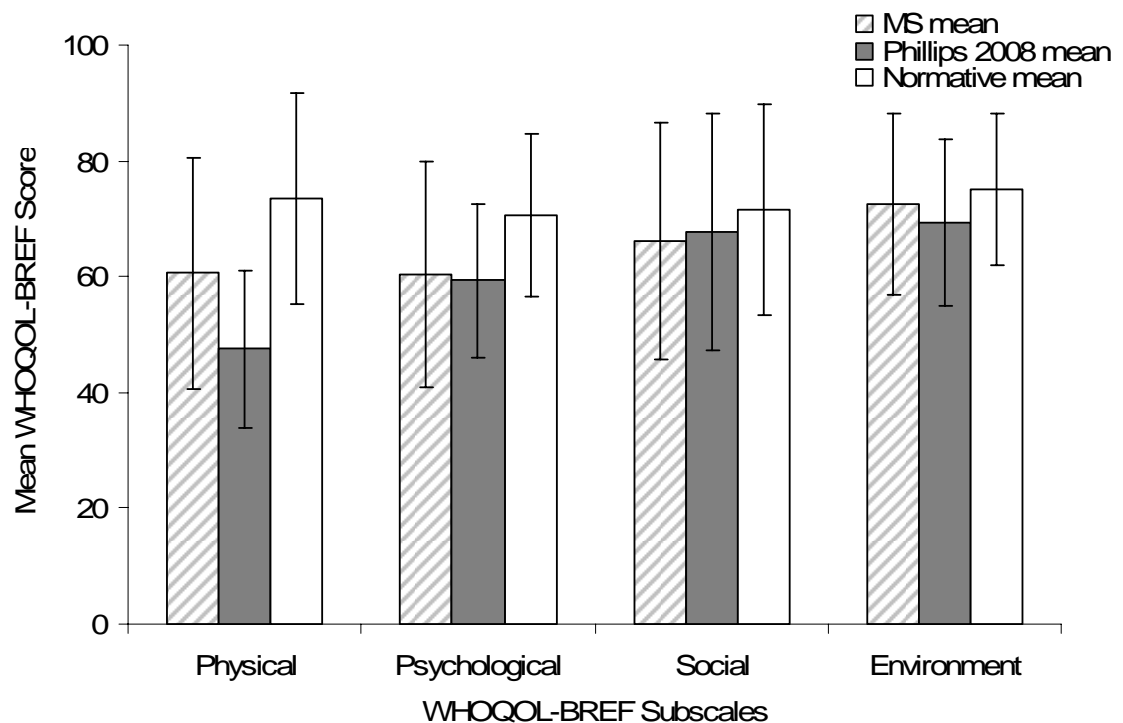


Figure 4.3 Mean WHO QoL-BREF scores for the current MS sample, the MS sample reported by Phillips et al., (2008) and a healthy, community-based population (n=866) published by Hawthorne et al., (2006). Error bars show standard deviation.

In addition to inclusion of a general QoL measure in the current study, an MS-specific QoL measure was deemed important because generic measures may not be sensitive to all areas of MS impact (Hobart et al., 2001). On the MSIS-29 the current MS group reported equivalent Physical and Psychological impact of MS. This pattern was somewhat different to that reported by Hobart et al., (2001), in which high Physical impact of MS was demonstrated. The current MS sample also reported overall reduced impact of MS compared to the Hobart sample. Once again, variability across samples, even when the same measure has been used, appears to be a fairly consistent feature.

4.2 Findings in Relation to Specific Hypotheses

The primary aim of this study was to explore associations between executive functioning abilities, ToM abilities, empathy and quality of life in a sample of individuals with MS. With this aim in mind, the decision was made to focus on recruiting and collecting data from an MS sample only, rather than also including a comparison group of healthy control participants.

4.2.1 Executive Function and Theory of Mind

It was hypothesised that reduced performance on executive functioning (EF) measures (Mental Flexibility, Inhibition and Response to Feedback) would be associated with lower performance on ToM tests (Eyes, Videos, Stories). Exploring performance on a range of EF and ToM tests provided the opportunity to potentially confirm and extend Henry et al's (2009) report of an association between impaired ToM performance on the Eyes Test and verbal fluency performance in their MS sample.

A significant positive correlation between composite measures of EF and ToM performance ($r=.55$) provided support for the hypothesis and association between these skills. Furthermore, the demonstration of this significant correlation in the absence of an association between EF and ToM performance, and a measure of speed of information processing, suggests that reduced speed of information processing does not account for the observed relationship. This finding is particularly relevant to an MS sample because of the reported impact of MS on processing speed (Litvan et al., 1988), which is frequently thought to impact negatively on other aspects of cognition, including executive function (Calabrese, 2006).

A significant positive association between performance on the Eyes Test and letter fluency ($r=.43$) confirmed the previous findings of Henry et al., (2009). They reported a larger association ($r=.65$) between Eyes ToM performance and their composite measure of letter and category fluency. It was not clear why the current association between ToM and Mental Flexibility was weaker, as using a composite measure of fluency did not increase the strength of association in the current sample. The two samples also appeared similar in terms of MS severity, disease duration, age and premorbid IQ. No reference was made to specific types of MS in the Henry et al., study, so this is may have been a factor.

After adjusting the significance level for multiple comparisons, there were no other significant relationships between Eyes performance and EF measures in the current sample (Inhibition $r=.29$, Response to Feedback $r=.37$, *ns*). This result

was somewhat surprising given the reported link between inhibitory control processes and ToM performance: evidenced by a reported association between reduced inhibitory control and ToM difficulties in ageing (Bailey & Henry, 2008) and schizophrenia (Shamay-Tsoory et al., 2008). Evidence for a negative impact on ToM performance as a consequence of concurrent engagement in an inhibitory test (Bull et al., 2008) further makes the current results somewhat surprising. Selection of inhibition measure and variability amongst people with MS may be relevant factors. It is possible that the tests used in the previous studies (CANTAB Intradimensional/Extradimensional shifting test and variants of 'No Go' tests) tapped aspects of inhibition more directly relevant to ToM performance.

A significant positive association was also found between ToM Stories performance and Response to Feedback ($r=.52$), suggesting involvement of shared processes for completion of these tests. Furthermore, partial correlations revealed that this association could not be attributed to MS severity. This finding extends those of Henry et al., (2009) by demonstrating an association between a different aspect of ToM performance and executive function ability. Exploration of ToM performance across a variety of different tests was important given evidence for impaired affect recognition in MS, and the effect this may have on the performance of people with MS on tests involving facial stimuli. Although the correlation between Mental Flexibility and Stories performance ($r=.33$, $p=.02$) did not reach significance after adjusting for multiple correlations, it represented a medium effect size and so suggests it may be useful to further explore the relationship between these abilities. Once again,

inhibition, as measured by the Hayling Test, was not significantly associated with ToM ability when measured according to understanding of short stories.

No significant relationships between performance on the ToM Videos Test and any of the executive functioning measures were found. This suggests that abilities required for successful performance on the Mental Flexibility, Inhibition and Response to Feedback measures were not particularly important for completion of the ToM Videos Test. This raises questions about what the Videos Test measures, as it may rely upon other aspects of cognition, such as memory, rather than ToM specifically. One feature of the Videos Test which distinguished it from the Eyes and Stories Tests was that presentation of videos meant that information was transitory (as in real life), compared to unlimited viewing times for the static Eyes photograph or Stories text. However, the lack of association between ToM performance and processing speed suggested that speed of information processing was not a significant factor in ToM performance here.

Overall, the findings in relation to Hypothesis 1 demonstrate a significant association between performance on two aspects of ToM, (Eyes Test - recognition and selection of emotional states based on partial pictures of faces; and the Stories Test - understanding of stories including faux pas, double bluffs, mistakes and white lies) and two separate, although probably related aspects of executive functioning, as measured by Mental Flexibility and Response to Feedback. Importantly, the results of partial correlations between ToM performance and executive functioning, after controlling for physical disability

indicated that the positive relationships between aspects of executive functioning and ToM performance could not be accounted for on the basis of MS severity. Furthermore, this relationship also could not be accounted for on the basis of participant age or premorbid IQ. These findings are theoretically relevant given questions about the mechanisms required for ToM abilities, as they provide further evidence suggesting partially shared mechanisms or process involved in these abilities. Furthermore, these findings are also clinically important given the evidence for impaired executive functioning in some people with MS (Drew et al., 2008), as this may be linked to impaired ToM abilities which have the potential to impact on aspects of social functioning. However, interpretation of these results are framed within the context of a lack of clear evidence in the sample for impaired ToM performance on some of these tests, and reliance on correlational analysis rather than a method which would allow more detailed interpretation of results, such as regression.

4.2.2 Executive Function (EF) and Empathy

The hypothesis that there would be a significant association between EF performance and empathy was based on the rationale that the ability to empathise requires cognitive abilities involving aspects of EF. Essentially, empathy involves affective, cognitive and motivational processes (Preston & DeWaal, 2002) and in order for a person to identify with another's emotional response, the cognitive ability to inhibit one's own perspective and mentally 'switch' between one's own and another's perspective is likely to be important. In particular, this study predicted an association between executive functioning and scores on the EQ and Perspective-Taking subscales of the IRI. A predicted

association between executive functioning performance and the other IRI scales was not made because these are thought to tap more affective aspects of empathy such as personal distress and empathic concern, rather than the more cognitive aspects of empathy such as perspective-taking and social rules. In terms of previous research findings, Benedict (2001) reported that performance on tests of executive functioning (WCST and Booklet Category Test) in people with MS (n=34) predicted lower empathy scores on the Hogan Empathy Scale. However, this finding has not been replicated and the generalisability of these results has been questioned because participants responded to adverts which specifically requested participation of individuals with MS experiencing “emotional problems”. A link between executive function and empathy is also relevant given reported evidence for both impaired executive functioning and empathy in autism (Baron-Cohen & Wheelwright, 2004; O’Hearn et al., 2009) and schizophrenia (Green, 2006; Montag et al., 2007).

The results produced preliminary and limited evidence for the hypothesis that impaired executive functioning would be associated with reduced empathy in this sample. There was a significant association between Mental Flexibility performance and the EQ questionnaire ($r=.30$), which measures aspects of perspective-taking, affective empathy and social skills (Lawrence et al., 2004). In the absence of a significant correlation between Mental Flexibility performance and the Perspective-Taking subscale of the IRI, the observed association with the EQ could reflect a specific aspect of perspective-taking (not tapped by the IRI Perspective-Taking subscale) or social skills. Performance on the other EF measures (Inhibition and Response to Feedback) did not correlate with any

empathy ratings. There was no association between performance on any EF measure and other-rater empathy ratings.

A possible explanation for the contradictory findings for differences between the present study's findings and those of Benedict et al., (2001) may relate to the selection of different empathy scales. The Hogan Empathy Scale has been criticised for having four relatively uncorrelated factors: social self-confidence, even-temperedness, sensitivity and nonconformity (Johnson et al., 1983), of which only sensitivity appears to be directly related to empathy (Davis, 1994). Questions about whether the results of the Benedict et al., (2001) study can be generalised have also been raised as discussed previously. Another important aspect of the results to consider in relation to the links between executive function and empathy is that (as discussed in Section 4.2.2), the MS sample as a whole did not demonstrate impaired empathy abilities according to either self or other-ratings. The possibility may be that the neural networks involved in empathy rely more on automatic processes, in line with the 'Simulation Theory' (Gallese, 2004) account, in which executive control is not a major influence. However, the considerable evidence from a range of research studies, in different patient groups and in healthy participants using imaging, would suggest some involvement of aspects of EF, particularly mental flexibility in empathy abilities (Decety & Jackson, 2004; Shamay-Tsoory et al., 2004). Although the sample size limited the type of analysis that was possible, there was no consistent evidence for an association between EF performance and empathy in this MS sample.

4.2.3 Executive Function (EF), Theory of Mind (ToM) and Quality of Life (QoL)

It was hypothesised that reduced executive functioning performance and reduced ToM performance would be associated with lower self-reported quality of life. In particular, that lower EF and ToM performance would be associated with lower Psychological and Social QoL (WHO QOL-BREF) and greater psychological impact of MS (MSIS-29). These predictions were based on the evidence where impaired EF has been previously shown to have a direct negative impact on QoL, and the assumption that impaired EF performance may be particularly likely to have a negative effect on Psychological and Social aspects of QoL - in part via aspects of social cognition such as ToM ability. The recent demonstration that attentional failures predicted all aspects of QoL in MS independently of disease severity further underlined the importance of cognitive factors for QoL in MS (Phillips et al., 2008). In addition, a relationship between impaired ToM and reduced social participation has been reported (Bora et al., 2006).

However, the results of the correlational analysis revealed that there were no significant associations between EF performance on the Mental Flexibility, Inhibition and Response to Feedback measures and self-reported QoL (WHO QOL-BREF, MSIS-29). Correlations between Mental Flexibility and the MSIS-29 Psychological subscale ($r = -.26$, $p = .05$), between Response to Feedback and Physical impact of MS ($r = -.26$, $p = .05$) as well as Inhibition and Environmental QoL ($r = .29$, $p = .040$) did not reach significance after adjusting for multiple comparisons. Thus, the results do not support the hypothesis that reduced

executive functioning is associated with reduced social and psychological QoL and greater psychological impact of MS. Furthermore, there were no significant correlations between ToM performance and QoL.

Previous research regarding EF performance and QoL in MS presents a variable picture. Some studies have reported that neuropsychological impairment, including executive functioning impairment, was associated with reduced QoL (e.g. Benito-Leon et al., 2002; Ryan et al., 2007). Others have reported a greater impact of physical factors on QoL and only weak relationships with cognitive function (Janardhan & Bajshi, 2000). In different studies, a link between executive functioning abilities and vocational status (rather than QoL) has been reported (Benedict et al., 2005; Rao et al., 1991), highlighting that there is the potential for executive dysfunction to impact on daily living (and thus aspects of QoL).

A further complication in interpreting negative findings is the tendency for negative results to remain unpublished: the 'file-drawer problem' (Rosenthal, 1979). This bias can make it difficult to gauge whether results are generalisable. The high correlations between self and other-report empathy ratings in this sample provide evidence supporting the validity of self-report in this group (although not directly for QoL measures), suggesting that the lack of association between executive functioning and QoL was not likely to be attributed to a lack of insight in this MS sample. A recent paper urges for caution in relation to the validity of self-report QoL ratings in MS after demonstrating low levels of agreement between self and other-ratings on the MSIS-29 (van der Linden,

2008). In their sample, other-ratings provided by close relatives appeared to significantly overestimate the disease impact of MS, whereas Healthcare providers underestimated disease impact compared to patient self-report. The researchers suggested that increased disability and possibly increased cognitive impairment (evidenced by a non-significant trend in the data) contributed to differences in patient and other-rater data. The sample in van der Linden's (2008) study had longer disease duration and higher levels of physical disability compared to the current sample.

In terms of QoL, it was notable that the current sample reported the psychological impact of MS as equivalent to the physical impact on the MS-specific MSIS-29. In addition, their rating of psychological quality of life was equivalent to physical quality of life on the WHO QOL-BREF subscales. Together these results emphasise the subjective importance of the psychological impact of MS on individuals. Although there is growing recognition of psychological consequences of MS, including relating to both cognition and mood (e.g. NICE, 2003), psychological aspects still receive less attention than the physical aspects (Foley & Brandes, 2009). Further work to raise awareness of psychological aspects of MS, and increase access to assessment and treatment remains an important policy aim and local objective.

4.3 Additional Research Questions

4.3.1 Insight in MS: Correspondence between Self and Other-rater Empathy Reports.

Given the evidence for executive impairment in MS and the links between executive function and frontal lobe systems, the issue of whether insight is affected in MS is pertinent. As already discussed above, the high correspondence between the self and other-ratings of empathy provided by this MS sample indicated that there was good agreement between MS participants and other-raters about their experiences in relation to empathy. This finding could be interpreted as suggesting that the MS participants had good insight into their experiences, although as discussed earlier, issues surrounding measurement of insight are complex. T-tests confirmed no significant differences between self and other-reports (all ns, $p > .05$).

There has been very little research into insight in MS that has used comparisons between self and other-reports. Unlike the current results, three of the four studies which have examined self and other-ratings in MS reported evidence of some discrepancies between information sources. Benedict et al., (2001) reported significant discrepancies between self and other-reports on the Hogan Empathy Scale in their MS sample, with MS participants providing higher self-ratings compared to other-raters: interpreted as evidence for reduced insight in the MS group. Warwick (2008) reported a significant difference between self and other-reports of impulsivity and memory on the Brock Adaptive Functioning Questionnaire, with MS participants reporting greater impairment in impulsivity and memory compared to other-rater reports. Randolphins et al.,

(2004) found increased self-reported memory complaints were associated with increased executive functioning difficulties, providing evidence for the veracity of self-report in MS. These findings should be interpreted in the context of concerns about the complexity of measuring insight using self and other-rater data, particularly, the important caveat that discrepancies between the two information sources do not necessarily indicate impaired insight on behalf of the person with MS (Snow et al., 2005).

Overall, the current results suggest that the participants in this MS sample had good insight into their empathy abilities and experiences, which would support the use of self-report measures in this group. In future studies, the question of whether a discrepancy between MS self-reports and other-rater reports may be linked to perception of greater impairment in MS participants compared to other-raters remains an interesting question.

4.3.2. Does MS affect cognitive empathy (ToM) and empathy differently?

One of the additional research questions this study aimed to address was regarding the impact of MS on ToM and empathy. It was expected that MS would be associated with impaired ToM, whereas empathy would remain relatively unaffected. This profile would be consistent with evidence from studies into ToM and empathy in schizophrenia (Shamay-Tsoory et al., 2007).

Overall, there was some evidence for impaired ToM performance on the Eyes Test, as the current MS sample's mean score was comparable to that reported by Henry et al., (2009), which was significantly lower than the score of their healthy

control group. Meanwhile, this sample did not demonstrate evidence of significantly lower empathy abilities on the basis of the EQ and IRI empathy scales compared to previously published data from healthy participants (Baron-Cohen & Wheelwright, 2004).

The pattern of the observed significant positive association between performance on the Eyes Test and the empathy scales thought to capture ToM (EQ and Perspective-Taking IRI subscale), compared to no clear association between ToM performance and empathy scales thought to capture affective empathy (Empathic Concern and Personal Distress IRI subscales) provides further evidence that MS may be associated with impaired ToM abilities and intact empathy. This profile was consistent with reported evidence of impaired ToM and intact affective empathy in Schizophrenia (Shamay-Tsoory et al., 2007).

4.4 Methodological Considerations

4.4.1 Recruitment

Recruitment to the MS group was guided by strict inclusion and exclusion criteria. This helped control for a number of factors that had the potential to confound the outcome including: age, history of neurological dysfunction separate to MS, history of psychiatric dysfunction separate to MS, intellectual functioning and visual perception. Potential participants with significant expressive language or visual impairments were not included within the sample.

The NART provided a general measure of estimated pre-morbid intellectual functioning. Although visual perception was not tested directly, potential participants with visual impairment were excluded by their Consultant Neurologist. Inclusion of a visual screening test may have been helpful although it would have increased the time for the assessment appointment. Strict inclusion criteria reduced the number of participants eligible to take part in the study, but also increased confidence that the results reported were a consequence of the key variables in the study rather than potentially confounding factors.

Recruitment was not limited to one MS sub-type in order to maximise the number of potential participants. As mentioned previously, there can be considerable variance within an MS subtype and the picture is further complicated by the movement of some people from one subtype to another during the course of their MS.

The overall response rate for taking part in the study was 20.2%, which was lower than expected and may have reflected several factors. Completion of the assessment appointment at a local hospital or the local MS Centre rather than visiting people in their own homes may have limited the opportunity for some people to participate. In particular, those with mobility difficulties, financial constraints and those experiencing symptoms of low mood or depression. Unfortunately, it was not possible to provide travel expenses for participants and Grampian covers a large geographical area. The 86 participants entered on the same healthcare database who took part in the previous Phillips et al., (2008) study into attention, emotion regulation and QoL in MS were excluded because they had already completed some of the experimental measures. This also reduced the number of potential participants.

4.4.2 Experimental Measures

4.4.2.1 Theory of Mind Tests

In terms of correlations between the ToM measures, there were significant correlations between the Eyes and Videos Tests, and between the Eyes and Stories Tests, but no significant association between the Videos and Stories Tests. This raises questions about whether these tests measure the same construct. Given that the tests involve decisions about a broad range of ToM aspects including mental states, emotions, intentions and logical thought, in the future it would be useful to develop tests that do not rely heavily on other aspects of cognition.

In the current sample, performance was superior for the control Videos and Stories Tests compared to the ToM versions, as would be expected. However performance on the Control Eyes Test was lower than on the Eyes Test. This pattern of results has been reported previously in a sample of 'Younger' and 'Older' participants (Slessor et al., 2007) and raises questions about the difficulty of the Control Eyes Test and whether it is an adequate control measure. The current Control Eyes Test was devised partly because the previous control version (which required participants to judge the gender of the person from a photograph of their eyes) was criticised for ceiling effects (Baron-Cohen et al., 2001). It may be that in aiming to avoid ceiling effects, the test has become too difficult.

4.4.2.2 Executive Function Tests

Selection of measures of executive function remains complex (Chan et al., 2008). In future studies, inclusion of executive functioning tests with greater ecological validity, such as the BADS, would be desirable: although they may have even greater confounds due to other cognitive components. However, the tests selected had good psychometric properties, were directly clinically relevant and provided useful clinical information in relation to the performance of the MS sample. The only significant correlation between these measures in this sample was between performance on the Mental Flexibility and Inhibition tests ($r=.43$), which likely reflects the role of inhibition in both tests. The lack of other significant correlations highlights the relative independence of separate elements of executive functioning and the importance of including a range of

executive functioning tests that cover each of these executive components (Drew et al., 2008).

4.4.2.3 Empathy Measures

The EQ and IRI empathy scales were selected because of their reasonable psychometric properties and ease of administration. The IRI has been shown to capture aspects of both 'cognitive' and 'affective' empathy in the different subscales, so this provided helpful additional information. The EQ and IRI have not been used in MS populations previously so using these measures provided useful new information on empathy in MS. Other-rater data provided additional information relating to insight in MS, important as few published studies have used other-ratings. The weak correlations between measures provided some support for Davis' (1980) claim that the IRI taps different aspects of empathy. The normative data for the IRI was from an American population, so the lack of culturally appropriate normative data was a limitation of the use of the IRI.

4.4.2.4 Quality of Life (QoL) Measures

Inclusion of a MS-specific measure of QoL was also important given the particular challenges that MS brings. The MSIS-29 was chosen because of its good psychometric properties which were based on a UK population, brief administration time and inclusion of both physical and psychological aspects. During completion of the current study the author became aware of an updated version of the MSIS-29 (version two) in which the response options were reduced from a 5-point scale to 4-point scale. It would perhaps have been preferable to use the version as it has superior psychometric properties (Hobart,

personal communication). The correlations between the QoL measures were generally consistent with the expected patterns of results, suggesting that these QoL measures were suitable for use with an MS sample.

4.4.2.5 Consideration of other measures

A clear limitation of the current study was the absence of specific information relating to neuropathological change in the MS participants who took part. Whilst neuroimaging would have been outwith the scope of the current study, future research would benefit from identifying links between ToM or executive functioning performance and underlying MS-related pathology.

4.5 Analysis

Detailed interpretation of the results from the current study was somewhat limited by the reliance on correlational analyses that can only determine association and not causation. The use of multiple regression analysis was considered to investigate how executive functioning could predict quality of life. However, this was not pursued partly because the sample size was not sufficient – a minimum of 66 participants is recommended (Gravetter & Wallnau, 1996) and partly because the results did not suggest that executive functioning was associated with quality of life in this sample.

4.5.1 Other Methodological Considerations

Since the aims of the current study focused on the possible relationships between executive functioning ability, ToM ability, mood and QoL in MS, the decision was taken to focus on recruiting an MS sample rather than also

recruiting a control group. Information about the performance of MS participants compared to controls on the Eyes Test, executive functioning tests and quality of life has already been reported by other separate studies (e.g. Henry et al., 2009; Rao et al., 1991; Wynia et al., 2008). Completion of the planned statistical analysis and further exploratory analysis highlighted that a decision to select participants on the basis of executive functioning, in order to recruit a group with executive functioning difficulties may have been more likely to demonstrate the predicted relationships. However, it was not possible to know this without first completing this study. The decision to include participants with a range of 'MS profiles' was important to achieve sufficient power in the current study. Future research could usefully focus more specifically on sub-groups of MS participants, for example, those with widespread executive function impairment.

4.6 Recommendations for Clinical Practice

Recommendations for clinical practice should be viewed in the context of the limitations of the study as outlined above. However the findings raise some important issues in relation to assessment and treatment of cognitive and psychological aspects of MS and suggest there is scope for positive change.

At present, it is recommended that people with MS have access to

“specialist neurological and neurological rehabilitation services...when they need them, usually when they develop any new symptom, sign, limitation on activities or other problem, or when their personal, family or social circumstances change” (NICE, 2003:7).

Another key priority within the NICE Guidelines is that

“health service workers in regular contact with people with MS should consider in a systematic way whether the person with MS has a ‘hidden’ problem contributing to their clinical situation, such as fatigue, depression, cognitive impairment, impaired sexual function or reduced bladder control” (NICE, 2003:9).

The current findings support the recent conclusions of Drew et al., (2008) that rates of executive function impairment in MS may be considerably higher than previously thought. In the current sample, 81% demonstrated some form of potential executive function impairment, which was even higher than the 66% reported by Drew et al., (2008). Despite the high rate of potential executive function impairment, to the author’s knowledge, none of the participants in the

current sample had been referred for neuropsychological assessment and consequently, none had received specialist neuropsychological assessment and treatment. This high rate of potential executive function impairment was particularly striking in a sample in which all participants were able to attend an appointment outwith their own home, in which 50% of participants were currently employed and in which there was a low rate of depression. As the participants in the current study appeared to be in better physical and psychological health than the general MS population, it seems reasonable to hypothesise that the participants who did not take part in the study may as a group have had higher rates of executive function impairment. Given the increasing evidence for effective treatment of cognitive impairment in MS, including some specific executive function impairments (e.g. Vogt et al., 2009), resources should be dedicated towards enabling MS sufferers to access services for assessment and treatment of cognitive difficulties. Early assessment seems preferable as it is likely that people with MS would find it easier to learn effective techniques and strategies at an earlier stage, while cognitive impairment is relatively mild.

The relatively high rates of anxiety observed in the current study highlight another potential need in MS patients. Although anxiety is referred to in the NICE Guidelines and psychologically-based treatments are mentioned in relation to severe anxiety, anxiety is not mentioned as part of the Key Priorities for Implementation. The growing research evidence highlighting anxiety as a consequence of MS should increase awareness of anxiety and provide further information regarding treatment. Although awareness of anxiety in MS appears

to be increasing, as evidenced by inclusion of anxiety in guidelines (e.g. NICE, 2003), greater access to treatment is still required (Bieske et al., 2008), particularly given the potential for effective anxiety treatment to impact positively on both psychiatric symptoms and cognitive abilities (Julian & Arnett, 2009).

In terms of quality of life in MS, the current sample reported a similar level of physical and psychological impact of MS, although at a lower level than reported previously in MS (Hobart et al., 2001). The current sample also reported equivalent levels of physical and psychological quality of life, which were impaired relative to normative data (Hawthorne et al., 2006). These results highlight that the move towards a greater recognition of the wide-ranging impact of MS on physical, psychological and social aspects of quality of life is vital.

4.7 Conclusions and Future Directions

The current study explored the associations between aspects of social cognition, executive function and quality of life in MS. Social cognition is emerging as a versatile approach for studying the interactions between social, cognitive and neural processes (Chan et al., 2008). Adopting an increasingly integrative approach to research in this area may be one valuable way of working to 'bridge the gaps' between assessment and everyday functioning.

Overall, the results demonstrated an association between aspects of ToM performance and executive function in MS. There was evidence of an association

between Mental Flexibility and one empathy measure (EQ) only. No clear relationships between ToM or executive function performance with self-reported QoL were demonstrated.

Although there was some evidence for impaired ToM, there was no evidence for impaired empathy abilities in this MS sample. Given the suggestion of valid self-report in this group, the evidence of equivalent Psychological and Physical QoL scores and the considerable levels of anxiety reported by some individuals, these factors could be interpreted as highlighting the need to recognise and address the psychological impact of MS with similar conviction to the physical impact.

The majority of participants (81%) demonstrated impaired executive functioning performance on at least one measure, which raises questions about whether there may be more widespread executive function impairment in MS than previously thought. This result highlights the importance of access to specialist neuropsychological assessment for people with MS. Furthermore, the high level of anxiety in this group emphasises the importance of ongoing research into the psychological and neuropsychological impact of MS.

Perhaps the most fitting conclusion is to reflect that, by its nature, MS does not offer clear pathways and neat explanations. The complex integration of physical, neurological and psychological aspects that are involved, bring unique challenges to individuals, and provide a fascinating and valuable area for continued research.

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Appendix 1

Invitation letter to potential participants

Letter of Invitation Social Cognition in Multiple Sclerosis

Dear

You are being invited to take part in a research study. Before you decide whether you are interested in taking part it is important for you to understand why the research is being done and what it will involve. The enclosed information sheet explains about the research project and includes contact details for the researchers if you wish to contact them to find out more information.

You have been contacted because your Consultant Neurologist thought that you may be appropriate to be contacted about the study and because your details are on the Department of Neurology Database of people with a diagnosis of Multiple Sclerosis.

After reading the Information Sheet, if you decide you are interested in hearing more about the study and may wish to take part, please complete the enclosed Contact Sheet and return it using the stamped, addressed envelope provided.

Once the contact sheet is received you will be telephoned within one week to ask whether you are interested in taking part.

If you have any questions please do not hesitate to contact us.

Yours sincerely

Consultant Neurologist

Ceri Trevethan
Trainee Clinical Psychologist
Dept. of Neuropsychology
Ward 40
Aberdeen Royal Infirmary
Aberdeen
Tel: 01224 556147
07870 516402 (after 5pm)

Dr Bruce Downey
Clinical Psychologist
Dept. of Neuropsychology
Ward 40
Aberdeen Royal Infirmary
Aberdeen
Tel: 01224 556147 or 554350

Appendix 2

Participant Information Sheet

Participant Information Sheet

1. Study title

Social Cognition in Multiple Sclerosis (MS): effects on cognition, mood and quality of life.

2. Invitation Paragraph

You are being invited to take part in a research study. Before you decide whether to take part it is important for you to understand why the research is being done and what it will involve. Please take time to read this information carefully and discuss it with others if you wish. Please ask us if there is anything which is not clear or if you would like more information. Take time to decide whether you wish to take part. Thank you for reading this.

3. What is the purpose of this study?

As part of my Doctorate training in Clinical Psychology I am carrying out a study that involves looking at the performance of people with Multiple Sclerosis on several different tasks. These tasks include general thinking skills and thinking skills used in social situations. The study also includes questionnaires about the impact of MS on your life, your quality of life and your mood.

The study plans to explore whether there are links between your general thinking skills, the thinking skills you use to understand social situations and your quality of life. We hope that the results should provide valuable information about the impact of MS on thinking skills and quality of life. Although there has been a lot of research into the physical changes associated with MS, it is important to explore the potential impact of MS on other aspects of everyday life, such as social functioning and quality of life.

If you take part in the study, the appointment for the tasks will take 60 minutes. Completing the questionnaires takes approximately 20 to 40 minutes. You can fill in the

questionnaires at home and return them using the stamped addressed envelope provided if this suits.

4. Why have I been chosen?

In order to investigate these issues we would like to recruit a group of people with MS, aged between 18 and 65. You are being asked to participate because you fit these criteria.

5. Do I have to take part?

No. It is up to you to decide whether to take part. If you do decide to take part, you will be given this information sheet to keep and will be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

6. What will happen to me if I take part?

You will be asked to attend an appointment at Woodend Hospital, Aberdeen or the Stuart Resource Centre, Aberdeen to complete 3 short tasks which look at your understanding of what other people think in social situations. 3 short tasks will then explore your general thinking skills. You will be asked to complete a short questionnaire which is used to assess your mood. You will be assessed on these tasks once. Completing these assessments should take no more than 60 minutes. You will be able to take breaks if you need to or complete the tasks during two appointments.

You will then be asked to complete 4 questionnaires either after your appointment or at home and return them by post (using the stamped, addressed envelope provided). These questionnaires explore how you understand what other people are feeling, your quality of life and the impact of MS on your life. If there are any questions you do not wish to answer you are free to leave them blank.

It will also be helpful if you would consider asking someone who knows you well to complete the two questionnaires about how you understand what other people are feeling. This is a standard way of measuring some aspects of empathy and social understanding. If you would prefer not to ask someone to complete these questionnaires you are free to decide this and do not need to give a reason.

7. What are the possible disadvantages and risks of taking part?

There are no known risks associated with taking part in this research study. During the assessment appointment, if you become tired or feel under stress, you are free to stop at any time, without providing a reason.

Unfortunately, it is not possible for participants to be compensated for their travel expenses.

8. What are the possible benefits of taking part?

There are no known immediate benefits to taking part in the research study. We hope that this study will provide useful information relating to social understanding in MS which may be used to guide future rehabilitation interventions.

9. What if something goes wrong?

If you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during this study, the normal National Health Service complaints mechanisms will be available to you.

10. Will my taking part be kept confidential?

All of your information will be kept strictly confidential. Any information about you which leaves the hospital will have your name and address removed so that you cannot be recognised from it.

All personal data collected will be destroyed after the study is finished.

11. What will happen to the results of the study?

The results from this study will be written up and submitted for academic review in line with my obligations as a Trainee Clinical Psychologist on the University of Edinburgh Clinical Psychology Doctoral course.

I will send you a summary of the main results of the study if you would like to receive this. I also plan to present the results of the study to people working in MS so that they can hear about the study. No participants will be identified in any publication or presentation.

12. Who is organising and funding the research?

This research is jointly organised by NHS Grampian and the University of Edinburgh.

13. Who has reviewed the study?

This study has been reviewed and approved by the North of Scotland Research Ethics Committee and the University of Edinburgh Clinical Psychology Ethics Committee.

14. Contact for further information

Should you require any further information please do not hesitate to contact me:

Ceri Trevethan, at Neuropsychology Department, Ward 40, Aberdeen Royal Infirmary, Aberdeen, AB25 2NZ

Or contact by telephone on 01224 556147 (9-5pm) or 07870 516402 (after 5pm).

Or by email on c.trevethan@nhs.net

You can also contact Dr Bruce Downey, Clinical Psychologist, Research Supervisor, at Department of Clinical Neuropsychology, Ward 40, Aberdeen Royal Infirmary, Aberdeen. Or by telephone on 01224 556147 or 01224 554350.

Thank you for considering taking part in this study.

Appendix 3

Consent Form

NHS Grampian

Ceri Trevethan
Trainee Clinical Psychologist
Department of Neuropsychology
Ward 40
Aberdeen Royal Infirmary
Foresterhill
Aberdeen AB25 2ZN
Telephone 01224 556147 (9-5)
07870 516402 (after 5pm)
E-mail c.trevethan@nhs.net



CONSENT FORM

Title of Project: Social Cognition in Multiple Sclerosis

Name of Researcher: Ceri Trevethan

Please initial box

- 1 I confirm that I have read and understand the information sheet dated (version) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
- 2 I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
- 3 I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐
- 4 I agree to take part in the above study. ☐

Name of Patient

Date

Signature

Researcher

Date

Signature

I would like to receive a summary of the results of the study (please circle) yes no

Appendix 4

Letter of approval from local NHS Research Ethics Committee

North of Scotland Research Ethics Committees

Summerfield House
2 Eday Road
Aberdeen
AB15 6RE

Telephone: 01224 558480
Facsimile: 01224 558609
Email: nosres@nhs.net



27 January 2009

Dr Ceri T Trevethan
Trainee Clinical Psychologist
NHS Grampian/ University of Edinburgh
Department of Clinical Neuropsychology
Ward 40
Aberdeen Royal Infirmary
Foresterhill
ABERDEEN
AB25 2NZ

Dear Dr Trevethan

Full title of study: Social cognition in Multiple Sclerosis: effects on cognition, mood and quality of life.
REC reference number: 09/S0802/1

Thank you for your letter of 17 January 2009 and email of 26 January 2009, responding to the Committee's request for further information on the above research and submitting revised documentation.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

The Committee has agreed that site-specific assessment is not required for the following site(s):

Research site	Name of PI (CTIMPs only) or local contact point
NHS Grampian	Dr Ceri Trevethan

The favourable opinion for the study therefore applies to the above site(s). There is no need to complete the Site-Specific Information Form or to inform other Research Ethics Committees about the research. However, all researchers and local research collaborators who intend to participate in this study at NHS sites should seek approval from the R&D office for the relevant care organisation.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Website > After Review.

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

09/S0802/1

Please quote this number on all correspondence

With the Committee's best wishes for the success of this project

Yours sincerely

Carol Irvine

PP

Dr Sheila A Simpson
Chair

Enclosures:

After ethical review – guidance for researchers

Appendix 5

Letter of approval from local Research and Development Office

Research and Development

Foresterhill House Annexe
Foresterhill
Aberdeen
AB25 2ZB



Dr C. Trevethan
Trainee Clinical Psychologist
NHS Grampian
Dept of Clinical Neuropsychology
Ward 40
Aberdeen Royal Infirmary

Date 18/02/09
Ethics Ref 09/S0802/1
R & D Ref 2009PC003

Enquiries to Louise Milne
Extension 53846
Direct Line 01224 553846
Email louise.milne2@nhs.net

Dear Dr Trevethan

Re: Social cognition in Multiple Sclerosis: effects on cognition, mood and quality of life.

Thank you very much for sending all relevant documentation. I am pleased to confirm that the project is now registered with the NHS Grampian Research & Development Office. The project has R & D Management Approval to proceed locally.

Please note that if there are any other researchers taking part in the project that are not named on the original Ethics application, please advise the Ethics Committee in writing and copy the letter to us so that we may amend our records and assess any additional costs.

Wishing you every success with your research

Yours sincerely

A handwritten signature in black ink that reads 'Louise Milne'.

Louise Milne
Data Co-ordinator

Appendix 6

Letter of indemnity provided by the University of Edinburgh



Edinburgh Clinical Trials Unit
The Queen's Medical Research Institute
47 Little France Crescent
Edinburgh, EH16 4TJ

Tel: 0131 242 9446
Email: ECTU@ed.ac.uk

24th November 2008

Dr Ceri Trevethan
Department of Clinical Neuropsychology
Aberdeen Royal Infirmary
Aberdeen
AB25 2NZ

Dear Dr Trevethan

REC Number: TO BE OBTAINED

**Study Title: Social cognition in Multiple Sclerosis: effects on cognition ,
mood and quality of life**

Under the requirements of the Scottish Executive Health Department's Research Governance Framework for Health and Community Care, the University of Edinburgh agrees in principle to act as Sponsor for this project. Sponsorship is subject to you obtaining a favourable ethical opinion and local NHS R&D management approval (if required).

As Chief Investigator, you must ensure that the study does not commence until all applicable approvals have been obtained. Following receipt of all relevant approvals, you should ensure that any amendments to the project are notified to the Sponsor, REC and relevant NHS R&D office(s).

Yours sincerely

Elspeth Currie
Research Governance Manager

ACCORD

Academic and Clinical Central Office for Research and Development



NHS
Lothian



edinburgh
bioQuarter

Appendix 7

Background Information Sheet

Background Information Sheet

Identifier

Gender.....

Age.....

Estimated total years of education.....
.....

Current occupation.....

Previous Occupation.....

Diagnosis Date.....

Onset of first
symptoms.....
.....

Type of MS.....

Handedness.....

Appendix 8

NART Word Sheet

National Adult Reading Test (NART)

SECOND EDITION

Word Card

Hazel E. Nelson

CHORD

ACHE

DEPOT

AISLE

BOUQUET

PSALM

CAPON

DENY

NAUSEA

DEBT

COURTEOUS

RAREFY

EQUIVOCAL

NAIVE

CATACOMB

GAOLED

THYME

HEIR

RADIX

ASSIGNATE

HIATUS

SUBTLE

PROCREATE

GIST

GOUGE

SUPERFLUOUS

SIMILE

BANAL

QUADRUPED

CELLIST

FACADE

ZEALOT

DRACHM

AEON

PLACEBO

ABSTEMIOUS

DETENTE

IDYLL

PUERPERAL

AVER

GAUCHE

TOPIARY

LEVIATHAN

BEATIFY

PRELATE

SIDEREAL

DEMESNE

SYNCOPE

LABILE

CAMPANILE



First published 1982, Second edition 1991

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Windsor, Berkshire, SL4 1DF, England.

Appendix 9

The Hayling Test Recording Sheet

Subject and test details

Name

Age

Date of test

Further details

The Hayling Sentence Completion Test

Score summary

Box A

Box B

Box C

Total scaled scores

+ + =

(Section 1 Scaled score) (Section 2 Scaled score) (Section 2 Errors scaled score)

Hayling Section 1: sensible completion

- In a moment I am going to read you a series of sentences, each of which has the last word missing from it. I want you to listen carefully to each sentence, and when I have finished each one, your job is to give me a word which completes the sentence. Do you understand?

Practice

- Before we start, I'll give you a couple of practice sentences so that you can get the hang of it. Are you ready?

P1 The rich child attended a private

P2 The crime rate has gone up this

Test

- OK, that's the end of the practice items. The next few sentences I'll read aren't really any more difficult than the two you've just done. But the important thing is that I want you to give me your answer as quickly as you can – the faster the better. Is that clear?

1 He posted a letter without a
or: He mailed a letter without a

2 In the first space enter your
or: In the first blank enter your

3 The old house will be torn

4 It's hard to admit when one is

5 The job was easy most of the

6 When you go to bed turn off the

7 The game was stopped when it started to

8 He scraped the cold food from his

9 The dispute was settled by a third

10 Three people were killed in a major motorway
or: Three people were killed in an interstate

11 The baby cried and upset her

12 George could not believe that his son had stolen a

13 He crept into the room without a

14 Billy hit his sister on the

15 Too many men are out of

Response

Time

Total time (raw score)

Scaled score (transfer this to box A in score summary above)

Table E

Total scaled scores	Overall scaled score	Classification
23	10	Very superior
22	9	Superior
21	8	Good
20	7	High average
17-19	6	Average
15-16	5	Moderate ave.
13-14	4	Low average
11-12	3	Poor
10	2	Abnormal
< 10	1	Impaired

Hayling overall scaled score

Table A

Raw score	Scaled score	Comment
0	7	High ave.
1-9	6	Average
10-18	5	Moderate ave.
19-22	4	Low ave.
23-50	3	Poor
51-60	2	Abnormal
>60	1	Impaired

Hayling Section 2: unconnected completion

- Now we are going to move on to the second section of the test. In this section I will read you a set of sentences with the last word missing just like the ones you have already done, but this time I want you to give me a word which does not fit at the end of the sentence – I want the word you give me to be completely unconnected to the sentence in every way. Do you understand?

Practice

- Before we start, I'll give you a couple of practice sentences so that you can get the hang of what is required.

P1 London is a very busy _____

P2 Her new shoes were the wrong _____

- If the subject makes an error refer to instructions in Manual (page 8).

Test

- 'OK, that's the end of the practice items. Remember that the words you give me must be unconnected to the sentence, and that it is important for you to give me your answer as quickly as you can. Are you ready?'

1 The captain wanted to stay with the sinking _____

2 They went as far as they _____

3 Most cats see very well at _____

4 Jean was glad the affair was _____

5 The whole town came to hear the mayor _____

6 Most sharks attack very close to _____

7 None of the books made any _____

8 The dough was put in the hot _____

9 She called the husband at his _____

10 All the guests had a very good _____

11 He bought them in the sweet
or: He bought them in the candy _____

12 His leaving home amazed all his _____

13 At last the time for action had _____

14 The dog chased our cat up the _____

15 At night they often took a short _____

Response

Time

Correct (unconnected)

Category A error (connected)

A score

Category B error (somewhat connected)

B score

Total Category A errors

A score

Total Category B errors

B score

1 3
2 6
3 10
4 14
5 18
6 24
7 30
8 36
9 42
10 48
11 54
12 60
13 66
14 72
15 78

1 1
2 2
3 3
4 4
5 9
6 14
7 19
8 24
9 29
10 34
>10 50

Total time (raw score)

Scaled score (transfer this to box B in score summary on page 1)

Total
Cat. A
errors

A score

Total
Cat. B
errors

B score

Converted score
(A score + B score)

Raw score	Scaled score	Comment
0	8	Good
1-2	7	High average
3-50	6	Average
51-60	5	Moderate ave.
61-100	4	Low average
101-120	3	Poor
121-130	2	Abnormal
> 130	1	Impaired

Converted score	Scaled score	Comment
0	8	Good
1-3	7	High average
4-9	6	Average
10-12	5	Moderate ave.
13-14	4	Low average
15-17	3	Poor
18-29	2	Abnormal
≥ 30	1	Impaired

Hayling 2 errors
scaled score
(transfer this to box
C in score summary
on page 1)

Appendix 10

The Brixton Test Recording Sheet

The Brixton Spatial Anticipation Test

- 'There are many pages here which all have the same basic design on them. There are always ten positions, and one of them is always coloured blue' [point to filled circle on page one]. 'However the coloured one moves around according to various patterns that come and go without warning. These numbers [point to numbers underneath the circles] are just here to refer to the position – there is nothing complicated or mathematical about this test'.
- 'Now, as I turn the pages over, your job is to pick up on the pattern as best you can, and point to where you think the blue one is going to be on the next page. It's not guess-work – you can work it out. For instance, imagine the blue one was here [point to position 6], and then when I turn the page it goes to 7, and then to 8, then to 9 – you might reasonably expect it next to go to 10'.
- 'From time to time the pattern changes without warning, and then it is your job to pick up on the new pattern as best you can. Do you understand?'
- Give further assistance if necessary
- 'Obviously the first time you have nothing to go on, so your first answer will have to be a guess – have a guess as to where the blue one will be next'

Item/ page	Correct answer	Subject's response	Correct/ incorrect
1	any		
2	3		<input type="checkbox"/>
3	4		<input type="checkbox"/>
4	5		<input type="checkbox"/>
5	6		<input type="checkbox"/>
6 *	7		<input type="checkbox"/>
7	4		<input type="checkbox"/>
8	3		<input type="checkbox"/>
9	2		<input type="checkbox"/>
10	1		<input type="checkbox"/>
11	10		<input type="checkbox"/>
12 *	9		<input type="checkbox"/>
13	10		<input type="checkbox"/>
14	5		<input type="checkbox"/>
15	10		<input type="checkbox"/>
16	5		<input type="checkbox"/>
17	10		<input type="checkbox"/>
18	5		<input type="checkbox"/>
19 *	10		<input type="checkbox"/>
20	7		<input type="checkbox"/>
21	8		<input type="checkbox"/>
22	9		<input type="checkbox"/>
23	10		<input type="checkbox"/>
24	1		<input type="checkbox"/>
25	2		<input type="checkbox"/>
26 *	3		<input type="checkbox"/>
27	10		<input type="checkbox"/>
28	9		<input type="checkbox"/>

Item/ page	Correct answer	Subject's response	Correct/ incorrect
29 *	8		<input type="checkbox"/>
30	1		<input type="checkbox"/>
31	2		<input type="checkbox"/>
32	3		<input type="checkbox"/>
33	4		<input type="checkbox"/>
34 *	5		<input type="checkbox"/>
35	4		<input type="checkbox"/>
36	10		<input type="checkbox"/>
37	4		<input type="checkbox"/>
38	10		<input type="checkbox"/>
39	4		<input type="checkbox"/>
40	10		<input type="checkbox"/>
41 *	4		<input type="checkbox"/>
42	9		<input type="checkbox"/>
43	9		<input type="checkbox"/>
44	9		<input type="checkbox"/>
45	9		<input type="checkbox"/>
46	9		<input type="checkbox"/>
47	9		<input type="checkbox"/>
48 *	9		<input type="checkbox"/>
49	9		<input type="checkbox"/>
50	8		<input type="checkbox"/>
51	9		<input type="checkbox"/>
52	8		<input type="checkbox"/>
53	9		<input type="checkbox"/>
54	8		<input type="checkbox"/>
55	9		<input type="checkbox"/>

Total number of errors
(raw score)

Scaled score

Table D		
Raw score	Scaled score	Classification
0-7	10	Very superior
8	9	Superior
9-10	8	Good
11-13	7	High average
14-17	6	Average
18-20	5	Moderate ave.
21-23	4	Low average
24-25	3	Poor
26-31	2	Abnormal
> 31	1	Impaired

Appendix 11

The Colour Trails Test 1



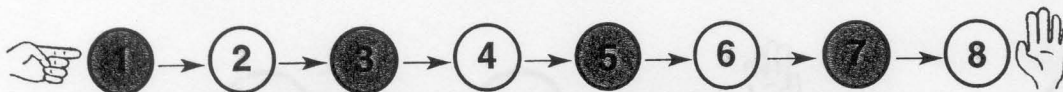
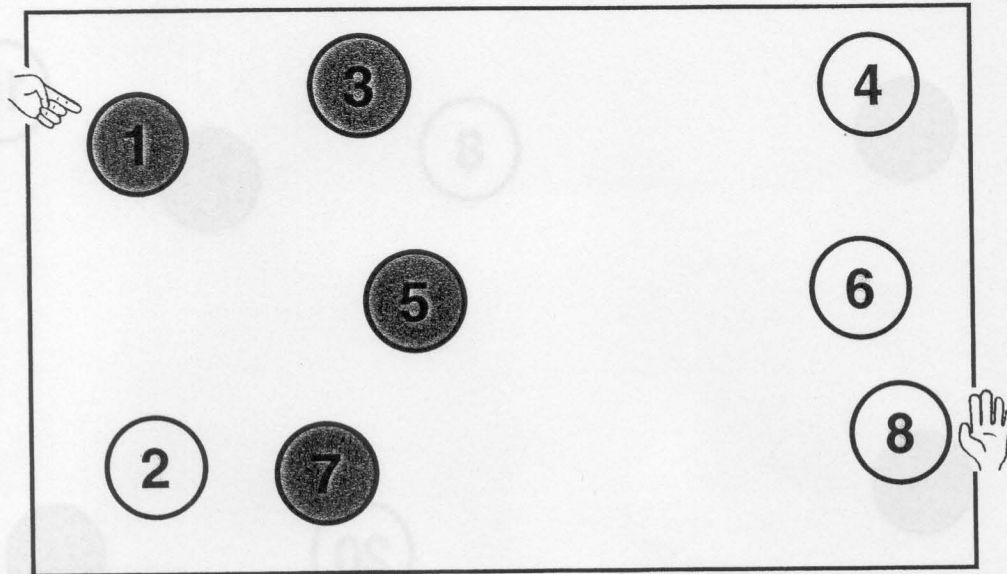
Color Trails I

Louis F. D'Elia, PhD, and Paul Satz, PhD

Form A

Name: _____

ID#: _____ Date: _____



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Name: _____
Date: _____



Appendix 12

The Hospital Anxiety and Depression Scale

Clinicians are aware that emotions play an important part in most illnesses. If your clinician knows about these feelings he or she will be able to help you more.

This questionnaire is designed to help your clinician know how you feel. Read each item below and **underline the reply** which comes closest to how you have been feeling in the past week. Ignore the number printed at the edge of the questionnaire.

Don't take too long over your replies, your immediate reaction to each item will probably be more accurate than a long, thought-out response.

A D

I feel tense or 'wound up'

- | | |
|---|---------------------------------|
| 3 | Most of the time |
| 2 | A lot of the time |
| 1 | From time to time, occasionally |
| 0 | Not at all |

I still enjoy the things I used to enjoy

- | | |
|---|--------------------|
| 0 | Definitely as much |
| 1 | Not quite so much |
| 2 | Only a little |
| 3 | Hardly at all |

I get a sort of frightened feeling as if something awful is about to happen

- | | |
|---|-----------------------------------|
| 3 | Very definitely and quite badly |
| 2 | Yes, but not too badly |
| 1 | A little, but it doesn't worry me |
| 0 | Not at all |

I can laugh and see the funny side of things

- | | |
|---|----------------------------|
| 0 | As much as I always could |
| 1 | Not quite so much now |
| 2 | Definitely not so much now |
| 3 | Not at all |

Worrying thoughts go through my mind

- | | |
|---|--------------------------|
| 3 | A great deal of the time |
| 2 | A lot of the time |
| 1 | Not too often |
| 0 | Very little |

I feel cheerful

- | | |
|---|------------------|
| 3 | Never |
| 2 | Not often |
| 1 | Sometimes |
| 0 | Most of the time |

I can sit at ease and feel relaxed

- | | |
|---|------------|
| 0 | Definitely |
| 1 | Usually |
| 2 | Not often |
| 3 | Not at all |

A D

I feel as if I am 'slowed down'

- | | |
|------------------------|---|
| Nearly all of the time | 3 |
| Very often | 2 |
| Sometimes | 1 |
| Not at all | 0 |

I get a sort of frightened feeling like 'butterflies' in the stomach

- | | |
|--------------|---|
| Not at all | 0 |
| Occasionally | 1 |
| Quite often | 2 |
| Very often | 3 |

I have lost interest in my appearance

- | | |
|---------------------------------------|---|
| Definitely | 3 |
| I don't take as much care as I should | 2 |
| I may not take quite as much care | 1 |
| I take just as much care as ever | 0 |

I feel restless as if I have to be on the move

- | | |
|------------------|---|
| Very much indeed | 3 |
| Quite a lot | 2 |
| Not very much | 1 |
| Not at all | 0 |

I look forward with enjoyment to things

- | | |
|--------------------------------|---|
| As much as I ever did | 0 |
| Rather less than I used to | 1 |
| Definitely less than I used to | 2 |
| Hardly at all | 3 |

I get sudden feelings of panic

- | | |
|-------------------|---|
| Very often indeed | 3 |
| Quite often | 2 |
| Not very often | 1 |
| Not at all | 0 |

I can enjoy a good book or radio or television programme

- | | |
|-----------|---|
| Often | 0 |
| Sometimes | 1 |
| Not often | 2 |
| Seldom | 3 |

Appendix 13

Disease Steps Scale

Disease Steps

METHODS: For Disease Steps, classification of a patient is determined by history and neurologic examination as well as course of MS. The scale consists of the following categories:

- ☐ **0 = Normal:** functionally normal with no limitations on activity or lifestyle. Patients may have minor abnormality on examination, such as nystagmus or an extensor plantar. The course is relapsing-remitting with a return to baseline with or without treatment. These patients are not treated with any ongoing symptomatic therapy for MS.
- ☐ **1 = Mild disability:** mild symptoms or signs. These patients have mild but definite findings such as sensory abnormalities, mild bladder impairment, minor incoordination, weakness, or fatigue. There is no visible abnormality of gait. The pattern of disease is relapsing-remitting, but patients may not have a full return to baseline following attacks. These patients may use ongoing symptomatic therapy such as amantadine, baclofen, or oxybutynin.
- ☐ **2 = Moderate disability:** the main feature is a visibly abnormal gait, but patients do not require ambulation aids. The pattern of disease is relapsing-remitting or progressive.
- ☐ **3 = Early cane:** intermittent use of cane (or other forms of unilateral support including splint, brace, or crutch). These patients use unilateral support primarily for longer distances, but are able to walk at least 25 feet without it. The pattern of disease is relapsing-remitting or progressive.
- ☐ **4 = Late cane:** these patients are dependent on a cane or other forms of unilateral support and cannot walk 25 feet without such support (eg, these patients may hang on to furniture inside their homes or touch the wall when walking in clinic). Patients may use a scooter for greater distances (eg, malls). The pattern of disease is relapsing remitting or progressive.
- ☐ **5 = Bilateral support:** patients require bilateral support to walk 25 feet (eg, two canes or two crutches or a walker). They may use a scooter for greater distances. The pattern of disease is relapsing-remitting or progressive.
- ☐ **6 = Confined to wheelchair:** patients are essentially confined to a wheelchair or scooter. They may be able to take a few steps but are unable to ambulate 25 feet, even with bilateral support. They may show further progression including worsening hand function or inability to transfer independently.
- ☐ **U = Unclassifiable:** this category is used for patients who do not fit the above classification (eg, significant cognitive or visual impairment, overwhelming fatigue, or significant bowel or bladder impairment in an otherwise minimally impaired patient).

Source: Hohol MJ, Orav EJ, Weiner HL. Disease steps in multiple sclerosis: a longitudinal study comparing disease steps and EDSS to evaluate disease progression. *Mult Scler.* 1999 Oct;5(5):349-54.

Appendix 14

The Empathy Quotient Questionnaire

THE CAMBRIDGE BEHAVIOUR SCALE

How to fill out the questionnaire

Below is a list of statements. Please read each statement very carefully and rate how strongly you agree or disagree with it by circling your answer. There are no right or wrong answers, or trick questions.

Examples

- | | | | | |
|--|---|---|--|--|
| E1. I would be very upset if I couldn't listen to music every day. | strongly agree | <input checked="" type="radio"/> slightly agree | slightly disagree | strongly disagree |
| E2. I prefer to speak to my friends on the phone rather than write letters to them. | strongly agree | slightly agree | slightly disagree | <input checked="" type="radio"/> strongly disagree |
| E3. I have no desire to travel to different parts of the world. | <input checked="" type="radio"/> strongly agree | slightly agree | slightly disagree | strongly disagree |
| E4. I prefer to read than to dance. | strongly agree | slightly agree | <input checked="" type="radio"/> slightly disagree | strongly disagree |
| | | | | |
| 1. I can easily tell if someone else wants to enter a conversation. | strongly agree | slightly agree | slightly disagree | strongly disagree |
| 2. I find it difficult to explain to others things that I understand easily, when they don't understand it first time. | strongly agree | slightly agree | slightly disagree | strongly disagree |
| 3. I really enjoy caring for other people. | strongly agree | slightly agree | slightly disagree | strongly disagree |
| 4. I find it hard to know what to do in a social situation. | strongly agree | slightly agree | slightly disagree | strongly disagree |

5. People often tell me that I went too far in driving my point home in a discussion.	strongly agree	slightly agree	slightly disagree	strongly disagree
6. It doesn't bother me too much if I am late meeting a friend.	strongly agree	slightly agree	slightly disagree	strongly disagree
7. Friendships and relationships are just too difficult, so I tend not to bother with them.	strongly agree	slightly agree	slightly disagree	strongly disagree
8. I often find it difficult to judge if something is rude or polite.	strongly agree	slightly agree	slightly disagree	strongly disagree
9. In a conversation, I tend to focus on my own thoughts rather than on what my listener might be thinking.	strongly agree	slightly agree	slightly disagree	strongly disagree
10. When I was a child, I enjoyed cutting up worms to see what would happen.	strongly agree	slightly agree	slightly disagree	strongly disagree
11. I can pick up quickly if someone says one thing but means another.	strongly agree	slightly agree	slightly disagree	strongly disagree
12. It is hard for me to see why some things upset people so much.	strongly agree	slightly agree	slightly disagree	strongly disagree
13. I find it easy to put myself in somebody else's shoes.	strongly agree	slightly agree	slightly disagree	strongly disagree
14. I am good at predicting how someone will feel.	strongly agree	slightly agree	slightly disagree	strongly disagree
15. I am quick to spot when someone in a group is feeling awkward or uncomfortable.	strongly agree	slightly agree	slightly disagree	strongly disagree
16. If I say something that someone else is offended by, I think that that's their problem, not mine.	strongly agree	slightly agree	slightly disagree	strongly disagree
17. If anyone asked me if I liked their haircut, I would reply truthfully, even if I didn't like it.	strongly agree	slightly agree	slightly disagree	strongly disagree

18. I can't always see why someone should have felt offended by a remark.	strongly agree	slightly agree	slightly disagree	strongly disagree
19. Seeing people cry doesn't really upset me.	strongly agree	slightly agree	slightly disagree	strongly disagree
20. I am very blunt, which some people take to be rudeness, even though this is unintentional.	strongly agree	slightly agree	slightly disagree	strongly disagree
21. I don't tend to find social situations confusing.	strongly agree	slightly agree	slightly disagree	strongly disagree
22. Other people tell me I am good at understanding how they are feeling and what they are thinking.	strongly agree	slightly agree	slightly disagree	strongly disagree
23. When I talk to people, I tend to talk about their experiences rather than my own.	strongly agree	slightly agree	slightly disagree	strongly disagree
24. It upsets me to see an animal in pain.	strongly agree	slightly agree	slightly disagree	strongly disagree
25. I am able to make decisions without being influenced by people's feelings.	strongly agree	slightly agree	slightly disagree	strongly disagree
26. I can easily tell if someone else is interested or bored with what I am saying.	strongly agree	slightly agree	slightly disagree	strongly disagree
27. I get upset if I see people suffering on news programmes.	strongly agree	slightly agree	slightly disagree	strongly disagree
28. Friends usually talk to me about their problems as they say that I am very understanding.	strongly agree	slightly agree	slightly disagree	strongly disagree
29. I can sense if I am intruding, even if the other person doesn't tell me.	strongly agree	slightly agree	slightly disagree	strongly disagree
30. People sometimes tell me that I have gone too far with teasing.	strongly agree	slightly agree	slightly disagree	strongly disagree
31. Other people often say that I am insensitive, though I don't always see why.	strongly agree	slightly agree	slightly disagree	strongly disagree

32. If I see a stranger in a group, I think that it is up to them to make an effort to join in.	strongly agree	slightly agree	slightly disagree	strongly disagree
33. I usually stay emotionally detached when watching a film.	strongly agree	slightly agree	slightly disagree	strongly disagree
34. I can tune into how someone else feels rapidly and intuitively.	strongly agree	slightly agree	slightly disagree	strongly disagree
35. I can easily work out what another person might want to talk about.	strongly agree	slightly agree	slightly disagree	strongly disagree
36. I can tell if someone is masking their true emotion.	strongly agree	slightly agree	slightly disagree	strongly disagree
37. I don't consciously work out the rules of social situations.	strongly agree	slightly agree	slightly disagree	strongly disagree
38. I am good at predicting what someone will do.	strongly agree	slightly agree	slightly disagree	strongly disagree
39. I tend to get emotionally involved with a friend's problems.	strongly agree	slightly agree	slightly disagree	strongly disagree
40. I can usually appreciate the other person's viewpoint, even if I don't agree with it.	strongly agree	slightly agree	slightly disagree	strongly disagree

Thank you for filling this questionnaire in.

Appendix 15

The Interpersonal Reactivity Index

INTERPERSONAL REACTIVITY INDEX

How to fill out the questionnaire

Below are a list of statements. Please read each statement very carefully and rate how strongly you agree or disagree with it by circling your answer. There are no right or wrong answers, or trick questions.

The following statements inquire about your thoughts and feelings in a variety of situations. For each item, indicate how well it describes you by choosing the appropriate letter on the scale at the top of the page: A, B, C, D, or E. When you have decided on your answer, fill in the letter next to the item number.

READ EACH ITEM CAREFULLY BEFORE RESPONDING.

Answer as honestly as you can. Thank you.

ANSWER SCALE:

A	B	C	D	E
DOES NOT DESCRIBE ME WELL				DESCRIBES ME VERY WELL

Examples:

1. I often look forward to going on holiday **E**
2. I sometimes find it difficult to concentrate on a book I am reading **C**

The following statements inquire about your thoughts and feelings in a variety of situations. For each item, indicate how well it describes you by choosing the appropriate letter on the scale at the top of the page: A, B, C, D, or E.

When you have decided on your answer, fill in the letter next to the item number. READ EACH ITEM CAREFULLY BEFORE RESPONDING. Answer as honestly as you can. Thank you.

ANSWER SCALE:

A	B	C	D	E
DOES NOT				DESCRIBES ME
DESCRIBE ME WELL				VERY WELL

1. I daydream and fantasize, with some regularity, about things that might happen to me. _____
2. I often have tender, concerned feelings for people less fortunate than me. _____
3. I sometimes find it difficult to see things from the "other guy's" point of view. _____
4. Sometimes I don't feel very sorry for other people when they are having problems. _____
5. I really get involved with the feelings of the characters in a novel. _____
6. In emergency situations, I feel apprehensive and ill-at-ease. _____
7. I am usually objective when I watch a movie or play, and I don't often get completely caught up in it. _____
8. I try to look at everybody's side of a disagreement before I make a decision. _____
9. When I see someone being taken advantage of, I feel kind of protective towards them. _____
10. I sometimes feel helpless when I am in the middle of a very emotional situation. _____
11. I sometimes try to understand my friends better by imagining how things look from their perspective. _____

12. Becoming extremely involved in a good book or movie is somewhat rare for me. _____
13. When I see someone get hurt, I tend to remain calm. _____
14. Other people's misfortunes do not usually disturb me a great deal. _____
15. If I'm sure I'm right about something, I don't waste much time listening to other people's arguments. _____
16. After seeing a play or movie, I have felt as though I were one of the characters. _____
17. Being in a tense emotional situation scares me. _____
18. When I see someone being treated unfairly, I sometimes don't feel very much pity for them. _____
19. I am usually pretty effective in dealing with emergencies. _____
20. I am often quite touched by things that I see happen. _____
21. I believe that there are two sides to every question and try to look at them both. _____
22. I would describe myself as a pretty soft-hearted person. _____
23. When I watch a good movie, I can very easily put myself in the place of a leading character. _____
24. I tend to lose control during emergencies. _____
25. When I'm upset at someone, I usually try to "put myself in his shoes" for a while. _____
26. When I am reading an interesting story or novel, I imagine how I would feel if the events in the story were happening to me. _____
27. When I see someone who badly needs help in an emergency, I go to pieces. _____
28. Before criticizing somebody, I try to imagine how I would feel if I were in their place. _____

Appendix 16

WHO QoL-BREF Questionnaire

WHOQOL-BREF

The following questions ask how you feel about your quality of life, health, or other areas of your life. I will read out each question to you, along with the response options. **Please choose the answer that appears most appropriate.** If you are unsure about which response to give to a question, the first response you think of is often the best one.

Please keep in mind your standards, hopes, pleasures and concerns. We ask that you think about your life **in the last four weeks.**

		Very poor	Poor	Neither poor nor good	Good	Very good
1.	How would you rate your quality of life?	1	2	3	4	5

		Very dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Very satisfied
2.	How satisfied are you with your health?	1	2	3	4	5

The following questions ask about **how much** you have experienced certain things in the last four weeks.

		Not at all	A little	A moderate amount	Very much	An extreme amount
3.	To what extent do you feel that physical pain prevents you from doing what you need to do?	5	4	3	2	1
4.	How much do you need any medical treatment to function in your daily life?	5	4	3	2	1
5.	How much do you enjoy life?	1	2	3	4	5
6.	To what extent do you feel your life to be meaningful?	1	2	3	4	5

		Not at all	A little	A moderate amount	Very much	Extremely
7.	How well are you able to concentrate?	1	2	3	4	5
8.	How safe do you feel in your daily life?	1	2	3	4	5
9.	How healthy is your physical environment?	1	2	3	4	5

The following questions ask about how completely you experience or were able to do certain things in the last four weeks.

		Not at all	A little	Moderately	Mostly	Completely
10.	Do you have enough energy for everyday life?	1	2	3	4	5
11.	Are you able to accept your bodily appearance?	1	2	3	4	5
12.	Have you enough money to meet your needs?	1	2	3	4	5
13.	How available to you is the information that you need in your day-to-day life?	1	2	3	4	5
14.	To what extent do you have the opportunity for leisure activities?	1	2	3	4	5

		Very poor	Poor	Neither poor nor good	Good	Very good
15.	How well are you able to get around?	1	2	3	4	5

		Very dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Very satisfied
16.	How satisfied are you with your sleep?	1	2	3	4	5
17.	How satisfied are you with your ability to perform your daily living activities?	1	2	3	4	5
18.	How satisfied are you with your capacity for work?	1	2	3	4	5
19.	How satisfied are you with yourself?	1	2	3	4	5

20.	How satisfied are you with your personal relationships?	1	2	3	4	5
21.	How satisfied are you with your sex life?	1	2	3	4	5
22.	How satisfied are you with the support you get from your friends?	1	2	3	4	5
23.	How satisfied are you with the conditions of your living place?	1	2	3	4	5
24.	How satisfied are you with your access to health services?	1	2	3	4	5
25.	How satisfied are you with your transport?	1	2	3	4	5

The following question refers to how often you have felt or experienced certain things in the last four weeks.

		Never	Seldom	Quite often	Very often	Always
26.	How often do you have negative feelings such as blue mood, despair, anxiety, depression?	5	4	3	2	1

Do you have any comments about the assessment?

[The following table should be completed after the interview is finished]

		Equations for computing domain scores	Raw score	Transformed scores*	
				4-20	0-100
27.	Domain 1	$(6-Q3) + (6-Q4) + Q10 + Q15 + Q16 + Q17 + Q18$ $\square + \square + \square + \square + \square + \square + \square$	a. =	b:	c:
28.	Domain 2	$Q5 + Q6 + Q7 + Q11 + Q19 + (6-Q26)$ $\square + \square + \square + \square + \square + \square$	a. =	b:	c:
29.	Domain 3	$Q20 + Q21 + Q22$ $\square + \square + \square$	a. =	b:	c:
30.	Domain 4	$Q8 + Q9 + Q12 + Q13 + Q14 + Q23 + Q24 + Q25$ $\square + \square + \square + \square + \square + \square + \square + \square$	a. =	b:	c:

* See Procedures Manual, pages 13-15

Appendix 17

The Multiple Sclerosis Impact Scale

Multiple Sclerosis Impact Scale (MSIS-29)

- The following questions ask for your views about the impact of MS on your day-to-day life **during the past two weeks**
- For each statement, please **circle** the **one** number that **best** describes your situation
- Please answer **all** questions

In the <u>past two weeks</u> , how much has your MS limited your ability to...	Not at all	A little	Moderately	Quite a bit	Extremely
1. Do physically demanding tasks?	1	2	3	4	5
2. Grip things tightly (e.g. turning on taps)?	1	2	3	4	5
3. Carry things?	1	2	3	4	5

In the <u>past two weeks</u> , how much have you been bothered by...	Not at all	A little	Moderately	Quite a bit	Extremely
4. Problems with your balance?	1	2	3	4	5
5. Difficulties moving about indoors?	1	2	3	4	5
6. Being clumsy?	1	2	3	4	5
7. Stiffness?	1	2	3	4	5
8. Heavy arms and/or legs?	1	2	3	4	5
9. Tremor of your arms or legs?	1	2	3	4	5
10. Spasms in your limbs?	1	2	3	4	5
11. Your body not doing what you want it to do?	1	2	3	4	5
12. Having to depend on others to do things for you?	1	2	3	4	5

In the <u>past two weeks</u> , how much have you been bothered with...	Not at all	A little	Moderately	Quite a bit	Extremely
13. Limitations in your social and leisure activities at home?	1	2	3	4	5
14. Being stuck at home more than you would like to be?	1	2	3	4	5
15. Difficulties in using your hands in everyday tasks?	1	2	3	4	5
16. Having to cut down the amount of time you spent on work or other daily activities?	1	2	3	4	5
17. Problems using transport (e.g. car, bus, train, taxi, etc.)?	1	2	3	4	5
18. Taking longer to do things?	1	2	3	4	5
19. Difficulty doing things spontaneously (e.g. not going out on the spur of the moment)?	1	2	3	4	5
20. Needing to go to the toilet urgently?	1	2	3	4	5
21. Feeling unwell?	1	2	3	4	5
22. Problems sleeping?	1	2	3	4	5
23. Feeling fatigued mentally?	1	2	3	4	5
24. Worries related to your MS?	1	2	3	4	5
25. Feeling anxious or tense?	1	2	3	4	5
26. Feeling irritable, impatient or short tempered?	1	2	3	4	5
27. Problems concentrating?	1	2	3	4	5
28. Lack of confidence?	1	2	3	4	5
29. Feeling depressed?	1	2	3	4	5

Please check that you have circled ONE number for EACH question
Thank you.

Appendix 18

Additional Information on Hayling and Brixton Test Performance

Additional Information on Hayling Test performance

Hayling Section 1 Scaled Scores*									
	1	2	3	4	5	6	7		
Number of Participants	0	0	3	1	7	28	3		
Sample Percentage (%)	0.0	0.0	7.1	2.4	16.7	66.7	7.1		
* 1 = Impaired, 2 = Abnormal, 3 = Poor, 4 = Low Average, 5 = Moderate Average, 6 = Average, 7 = Above Average									
Hayling Section 2 Scaled Scores*									
	1	2	3	4	5	6	7	8	
Number of Participants	1	0	2	11	6	21	1	0	
Sample Percentage (%)	2.4	0.0	4.8	26.2	14.3	50.0	2.4	0.0	
* 1 = Impaired, 2 = Abnormal, 3 = Poor, 4 = Low Average, 5 = Moderate Average, 6 = Average, 7 = High Average, 8 = Good									
Number of Hayling Category A Errors									
	0	1	2	3	4	5	6	7	8
Number of Participants	14	9	9	3	4	1	1	0	1
Sample Percentage (%)	33.3	21.4	21.4	7.1	9.5	2.4	2.4	0.0	2.4
Number of Hayling Category B Errors									
	0	1	2	3	4	5	6	7	8
Number of Participants	7	9	3	5	5	4	5	2	2
Sample Percentage (%)	16.7	21.4	7.1	11.9	11.9	9.5	11.9	4.8	4.8
Hayling Section 2 Total Response Error Scaled Scores*									
	1	2	3	4	5	6	7	8	
Number of Participants	4	7	2	1	2	10	11	5	
Sample Percentage (%)	9.5	16.7	4.8	2.4	4.8	23.8	26.2	11.9	

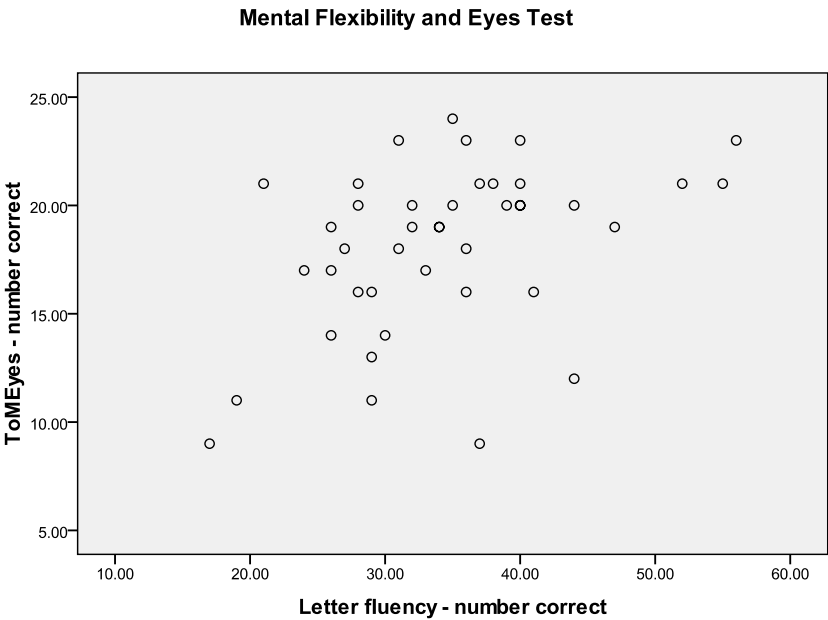
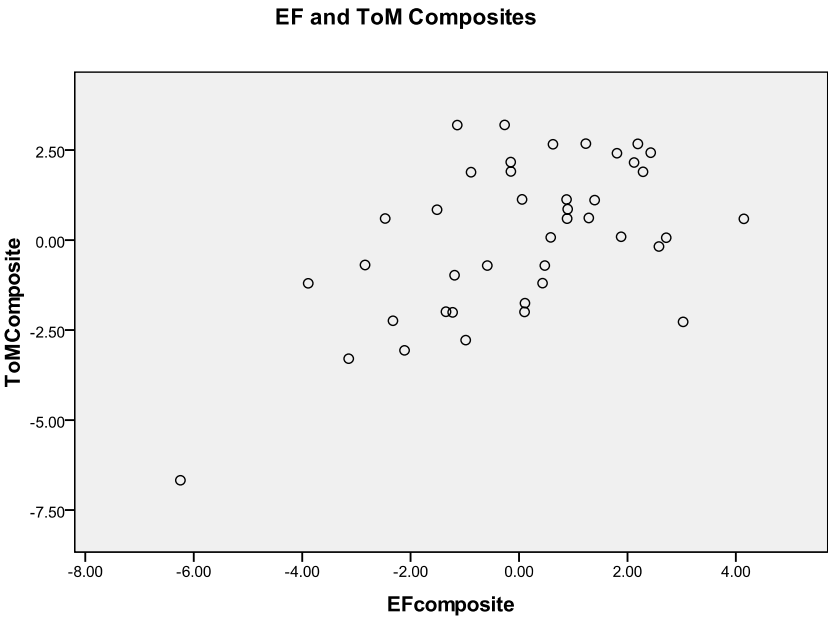
Additional Information on Brixton Test performance

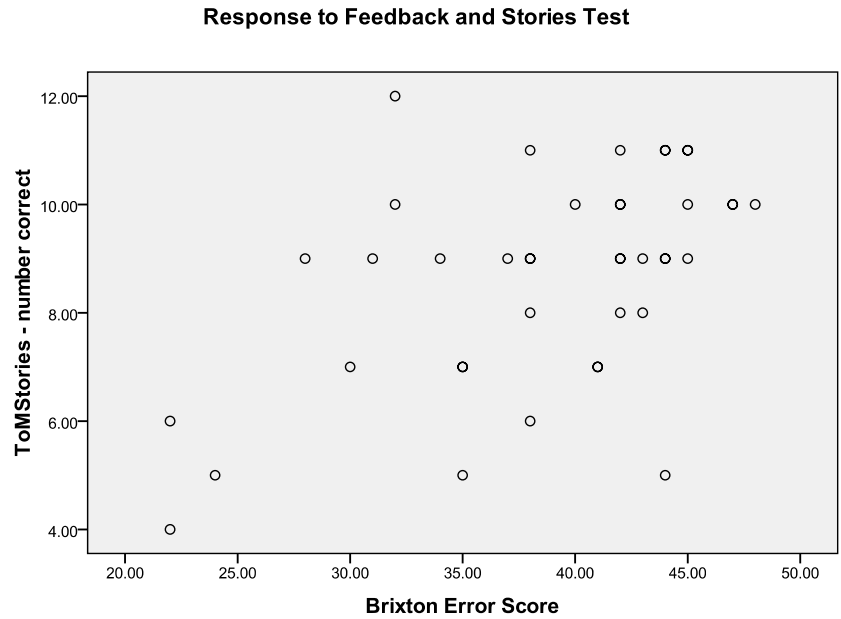
Brixton Error Scaled Scores*										
	1	2	3	4	5	6	7	8	9	10
Number of Participants	2	2	2	4	4	8	14	5	1	0
Sample Percentage (%)	4.8	4.8	4.8	9.5	9.5	19.0	33.3	11.9	2.4	0.0
* 1 = Impaired, 2 = Abnormal, 3 = Poor, 4 = Low Average, 5 = Moderate Average, 6 = Average, 7 = High Average, 8 = Good, 9 = Superior, 10 = Very Superior										

Appendix 19

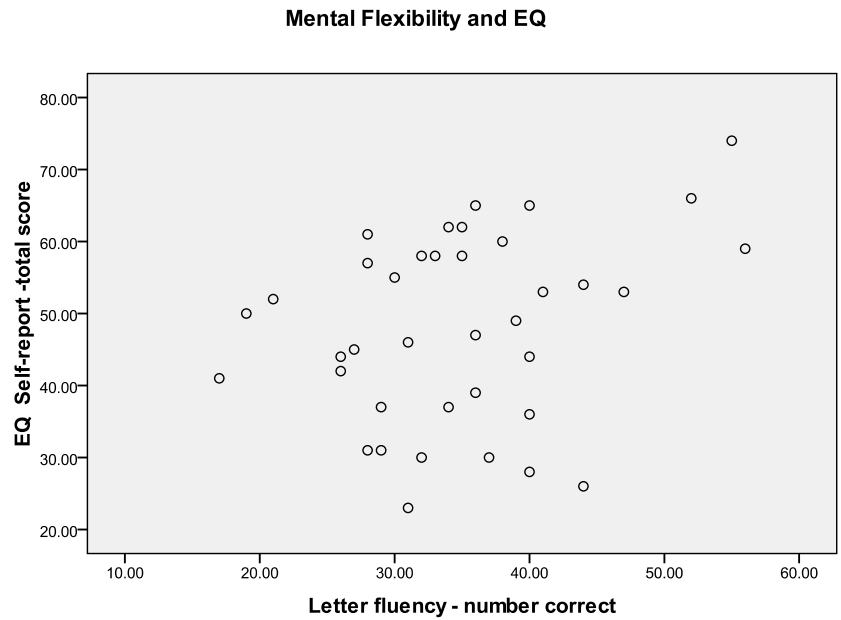
Scatterplots of Data Relating to Hypotheses

Hypothesis 1: Association between EF and ToM Measures

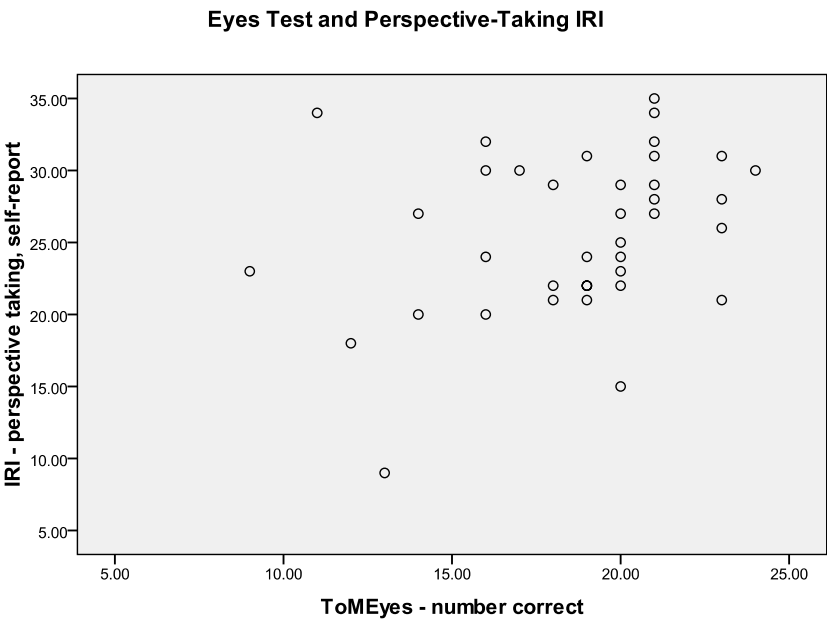




Hypothesis 2: Association between EF and Empathy



Additional Research Question: ToM and Empathy



Appendix 20

Table of Correlations for Other Relationships of Interest

Executive Function Performance and Control ToM Test Performance

	Mental Flexibility	Inhibition	Response to Feedback	Processing Speed
Control Eyes Test	.146	.209	.258	-.107
Control Videos Test	.128	.188	.256	-.138
Control Stories Test	.354* (p=.023)	.062	.266	-.109

Executive Function Performance and Other-Rater Empathy Ratings

	Other-Rater Empathy Measures		Remaining IRI subscales		
	EQ (n=38)	IRI Perspective-Taking (n=38)	IRI Empathic Concern (n=38)	IRI Personal Distress (n=38)	IRI Fantasy (n=38)
Mental Flexibility	-.011	-.096	-.108	-.222	-.049
Inhibition	.065	-.108	-.120	.002	-.039
Response to Feedback	.143	.044	.164	-.018	.021

all ns

Correlations between Executive Function Measures

EF Measures	Correlation
Mental Flexibility and Inhibition	.434**
Mental Flexibility and Response to Feedback	.001
Inhibition and Response to Feedback	.232

** p < .001

Correlations between ToM Measures

ToM Measures	Correlation
Eyes and Videos	.381*
Eyes and Stories	.483**
Stories and Videos	.040

** sig. p < .001, * sig p < .05

Correlations between Control ToM Measures

Control ToM Measures	Correlation
Eyes and Videos	.030
Eyes and Stories	.222
Stories and Videos	.216

ns

Correlations between ToM and Control Measures

Control and ToM Versions	Correlation
ToM Eyes and Control Eyes	.176
ToM Videos and Control Videos	.213
ToM Stories and Control Stories	.484**

** sig. p < .001

Correlations between Empathy Self-Report Measures

Self-Report Empathy Measures	Correlation
EQ and Perspective-Taking	.691**
EQ and Empathic Concern	.609**
EQ and Personal Distress	-.154
EQ and Fantasy	.174
Perspective-Taking and Empathic Concern	.593**
Perspective-Taking and Personal Distress	.037
Perspective-Taking and Fantasy	.278
Empathic Concern and Personal Distress	.161
Empathic Concern and Fantasy	.305
Personal Distress and Fantasy	-.145

** sig. p < .001

Correlations between Empathy Other-Rater Measures

Other-Report Empathy Measures	Correlation
EQ and Perspective-Taking	.738**
EQ and Empathic Concern	.624**
EQ and Personal Distress	-.383*
EQ and Fantasy	.345
Perspective-Taking and Empathic Concern	.611**
Perspective-Taking and Personal Distress	-.360
Perspective-Taking and Fantasy	.161
Empathic Concern and Personal Distress	-.100
Empathic Concern and Fantasy	.352*
Personal Distress and Fantasy	.033

** sig. p < .001, * sig. p < .05

Correlations between Self-Report QoL Measures

Self-Report Quality of Life Measures and Disease Steps			Correlation
WHOQOL-BREF Physical	&	WHOQOL-BREF Psychological	.489**
WHOQOL-BREF Physical	&	WHOQOL-BREF Social Relations	.253, ns
WHOQOL-BREF Physical	&	WHOQOL-BREF Environment	.426, ns
WHOQOL-BREF Physical	&	MSIS-29 Physical	-.770**
WHOQOL-BREF Physical	&	MSIS-29 Psychological	-.648**
WHOQOL-BREF Physical	&	WHOQOL-BREF Social Relations	.489**
WHOQOL-BREF Psychological	&	WHOQOL-BREF Environment	.556**
WHOQOL-BREF Psychological	&	MSIS-29 Physical	-.315, ns
WHOQOL-BREF Psychological	&	MSIS-29 Psychological	-.609**
WHOQOL-BREF Social Relations	&	WHOQOL-BREF Environment	.751**
WHOQOL-BREF Social Relations	&	MSIS-29 Physical	-.138, ns
WHOQOL-BREF Social Relations	&	MSIS-29 Psychological	-.492**
WHOQOL-BREF Environment	&	MSIS-29 Physical	-.280, ns
WHOQOL-BREF Environment	&	MSIS-29 Psychological	-.618**
MSIS-29 Physical	&	MSIS-29 Psychological	.602**
WHOQOL-BREF Physical	&	Disease Steps	.464, ns
WHOQOL-BREF Psychological	&	Disease Steps	-.147, ns
WHOQOL-BREF Social Relations	&	Disease Steps	-.157, ns
WHOQOL-BREF Environment	&	Disease Steps	-.165, ns
MSIS-29 Physical	&	Disease Steps	.784**
MSIS-29 Psychological	&	Disease Steps	.275, ns

** sig. p < .001, * sig. p < .05

Correlations between HADS scores and Executive Function Measures

Mood and EF Measures	Correlations
Anxiety & Mental Flexibility	-.341*
Anxiety & Inhibition	-.081
Anxiety & Response to Feedback	.061
Depression & Mental Flexibility	-.185
Depression & Inhibition	-.209
Depression & Response to Feedback	-.145

** sig. p < .001, * sig. p < .05

Correlations between HADS Scores and QoL Measures

Mood and QoL Measures	Correlations
Anxiety & Physical QoL	-.202
Anxiety & Psychological QoL	-.566**
Anxiety & Social QoL	-.371*
Anxiety & Environment QoL	-.513**
Anxiety & Physical MS Impact	-.103
Anxiety & Psychological MS Impact	.497
Depression & Physical QoL	-.526**
Depression & Psychological QoL	-.704**
Depression & Social QoL	-.578**
Depression & Environment QoL	-.654**
Depression & Physical MS Impact	-.346*
Depression & Psychological MS Impact	.589

** sig. p < .001, * sig. p < .05

Correlations between Disease Steps and QoL Measures

MS Severity and QoL	Correlations
Severity & Physical QoL	-.464*
Severity & Psychological QoL	-.147
Severity & Social QoL	-.157
Severity & Environment QoL	-.165
Severity & Physical MS Impact	.784**
Severity & Psychological MS Impact	.275

** sig. p < .001, * sig. p < .01